UNIVERSIDADE DE LISBOA
FACULDADE DE MEDICINA

THE IMPACT OF RHEUMATIC DISEASES ON EARLY RETIREMENT

PEDRO ALMEIDA LAIRES

ORIENTADORES: PROF. DOUTOR MIGUEL REBORDÃO DE ALMEIDA GOUVEIA
PROF. DOUTORA HELENA CRISTINA DE MATOS CANHÃO
PROF. DOUTOR JOÃO EURICO CABRAL DA FONSECA

TESE ESPECIALMENTE ELABORADA PARA OBTENÇÃO DO GRAU DE DOUTOR EM CIÊNCIAS E TECNOLOGIAS DA SAÚDE (EPIDEMIOLOGIA)

2017

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2017

A IMPRESSÃO DESTA TESE FOI APROVADA PELO CONSELHO CIENTÍFICO DA FACULDADE DE MEDICINA DE LISBOA EM REUNIÃO DE 22 DE NOVEMBRO DE 2016

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LIST OF ACRONYMS

ACR – American College of Rheumatology

Anti-TNF – Anti-Tumor Necrosis Factor

BMI – Body Mass Index

BSRBR - British Society for Rheumatology Biologics Register

CAGR - Compound Annual Growth Rate

CI – Confidence Interval

COPCORD – Community Oriented Program of Control of Rheumatic Diseases

CoReumaPt - The Portuguese Cohort of Rheumatic Diseases

CORRONA - Consortium of Rheumatology Researchers of North America

CV - Cardiovascular

DALY – Disability-Adjusted Life Years

DMARD - Disease-Modifying Antirheumatic Drug

EpiReumaPt – Portuguese Epidemiologic Study of Rheumatic Diseases

EQ-5D – European Quality of life Questionnaire

EU – European Union

GBD – Global Burden of Disease

GDP – Gross Domestic Product

GRADE - Grading of Recommendations, Assessment, Development and Evaluations

HAQ – Health Assessment Questionnaire

HiAP - Health in All Policies

HTA - Health Technology Assessment

INS – *Inquérito Nacional de Saúde* (National Health Survey)

IR – Inactivity Ratio

KOOS – Knee injury and Osteoarthritis Outcome Score

LBP – Low Back Pain

MI – Myocardial Infarction

MSK – Musculoskeletal

NDB - National Data Bank for Rheumatic Diseases

NHS - National Health Service

NHIS - National Health Interview Survey

NPHS - Canadian National Population Health Survey

NSAIDs – Non-Steroid Anti-Inflammatory Drugs

NUTS – Nomenclature of Territorial Units for Statistics

OA – Osteoarthritis

OECD – Organisation for Economic Co-operation and Development

OP – Osteoporosis

OR – Odds-Ratio

PAF – Population Attributable Fraction

PNS - *Plano Nacional de Saúde* (National Health Plan)

PSU – Primary Sampling Unit

PYWLL – Potential Years of Working Life Lost

QoL – Quality of Life

RA – Rheumatoid Arthritis

RCT – Randomized Clinical Trial

RD – Rheumatic Diseases

SD – Standard Deviation

SF-36 – Short-Form Health Survey

SHARE – Survey of Health, Ageing, and Retirement in Europe

SPR – *Sociedade Portuguesa de Reumatologia* (Portuguese Society of Rheumatology)

UK – United Kingdom

USA – United States of America

VIF – Variance Inflation Factor

WHO – World Health Organization

WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index

YLD – Years Lived with Disability

YWLL – Years of Working Life Lost

ACKNOWLEDGEMENTS

Cumpre-me manifestar publicamente, por dever de gratidão, o meu reconhecimento a todos os que, directa ou indirectamente, ajudaram a cumprir este trabalho e esta importante etapa da minha vida.

O meu primeiro agradecimento recai naturalmente sobre quem considero irremediavelmente determinante na execução deste Doutoramento, o Professor Miguel Gouveia. Não há qualquer exagero em dizer que sem a sua ajuda este projecto não teria sido possível concretizar. A raiz desta Tese parte da sua cabeça, donde aliás brota um invejável sem-número de ideias. Tenho dificuldade em me recordar de um único contacto com o Professor Miguel Gouveia em que não tenha havido um pensamento ou uma reflexão sem admirável substância. Apesar de ter uma inteligência difícil de acompanhar, é uma pessoa com quem sabe muito bem conviver, porque tem a força rara da Sinceridade de Montesquieu.

Agradeço também toda a Orientação dada pela Professora Helena Canhão, que aceitou generosamente a função, que soube encaixar numa super-agenda. Apesar do seu ritmo imparável, consegui encontrar em si um equilíbrio notável de rigor e pragmatismo. Todas as orientações que me deu foram úteis e relevantes.

Ao Professor João Eurico da Fonseca que também aceitou, já numa fase mais tardia, a Orientação desta Tese, onde desde logo começou a contribuir significativamente. É, como sempre, um grande exemplo que sabe bem ter por perto. Estou certo que Stephen Covey encontraria em si um excelente *case study* de eficiência.

Agradeço ao Professor Jaime Branco, que me convidou a participar no estudo EpiReumaPt. Estimo a confiança que depositou na minha pessoa e agradeço a inspiração que decorre da sua inesgotável energia e perseverança.

À Professora Ana Paula Martins por todo o suporte e incentivo que me prestou ao longo de praticamente todo o Doutoramento. Não fosse aquele derradeiro "empurrão" nas Jornadas da ANDAR e, provavelmente teria permanecido quedado *sine die* no seio da indecisão.

Ao Dr. Luís Rocha que sempre apoiou o meu caminho de investigação epidemiológica. É um bom amigo e um dos meus mentores profissionais com quem aprendo sempre.

Agradeço ao Professor Paulo Nicola tudo o que me ensinou, bem como o contágio pela paixão da epidemiologia. E já agora aos meus alunos do Mestrado de Epidemiologia da Faculdade de Medicina que coadjuvaram na reincidência desta paixão (que deveria ser mais epidémica), durante um período crucial do meu Doutoramento.

Tentando ser mais breve nos considerandos, mas não menos grato, quero ainda destacar o apoio do Professor Pedro Aguiar pelos seus conselhos estatisticamente e intelectualmente significativos. Quero também nomear o apoio técnico mais pontual do Professor Baltazar Nunes, da Drª. Ana Rodrigues e da Drª. Mónica Eusébio e agradecer os debates técnicos, nomeadamente em torno do Stata em modo *survey* – existem indubitavelmente debates mais estimulantes a ter na vida, mas estes não deixaram de ser úteis. Agradeço à equipa de investigação EpiReumaPt, que acolheu uma pessoa que dificilmente consegue distinguir uma entesite de uma dactilite.

Agradeço ainda a diferentes pessoas que ao longo da minha vida foram determinantes na visão que tenho do mundo e portanto também aqui merecem um destaque especial. Ao meu avô Almeida que teve osteoartrose, reforma antecipada e um coração do tamanho do mundo. À France pelo carinho, pela poesia e por me ensinar que ainda há caminho para o lirismo no meio do pragmatismo seco do dia-a-dia. Ao Álvaro Couto pelo romantismo fervoroso, pela coragem e irreverência que sempre me comoveu. Ao Sagara Priya pela orientação espiritual, que não é bafienta, nem *new age*; à Joaninha porque continua a ser um *enhancer* da minha felicidade; e aos meus amigos que são a família escolhida e que me fazem sentir bem.

Por fim, agradeço às pessoas mais importantes e a quem dedico esta Tese e para quem as palavras serão sempre poucas – Ao meu pai, à minha mãe e ao meu querido irmão.

ABSTRACT

BACKGROUND: Rheumatic Diseases (RD) are characterized by pain and reduction in the range of motion and function in one or more areas of the musculoskeletal system. RD are prominent causes of morbidity and disability throughout the world, giving rise to enormous healthcare expenditures. RD may also lead to early retirement, generating indirect costs to society, namely through its most prevalent nosologic entity, osteoarthritis (OA).

OBJECTIVES: This study primarily aimed: 1) To examine the association between RD and early retirement in the Portuguese population; 2) To measure the productivity loss associated with early retirement attributable to RD in Portugal; and 3) To review possible effective interventions targeting early retirement due to RD.

METHODS: In order to achieve these objectives individual level data from two national, cross-sectional, population-based surveys were used - the National Health Survey, conducted in 2005-2006 (INS) and the first nationwide study on RD, conducted in 2011-2013 (EpiReumaPt). Both surveys had samples considered to be representative of the regions of mainland Portugal (North, Center, Lisbon region, Alentejo, and Algarve) and the autonomous regions of the Azores and Madeira. All participants aged between 50 and 64 years old, approaching the statutory pension age, were included in the analysis (INS: 3762 men and 4241 women; EpiReumaPt: 1065 men and 1727 women). The presence of RD was based on self-report by the surveys' participants. Due to its prevalence and associated disability a special interest was devoted to OA, which was defined by the clinically diagnosis of OA initially done by a rheumatologist in a patient interview and further validated by other 3 experienced rheumatologists in the EpiReumaPt study, according with the American College of Rheumatology (ACR) classification criteria. Regarding the main dependent variable, a *lato* and *stricto sensu* definition of premature job loss was adopted, which enabled taking into consideration the existence of different pathways to early retirement. In addition, anticipated retirement due to RD directly reported by the EpiReumaPt participants was analysed. Other variables of interest, in particular those potentially influencing early retirement, were described and analysed as well. These included sociodemographic, ill-health, lifestyle, and socioeconomic factors. The effects of self-reported RD and OA on the likelihood of early retirement were

obtained at the individual level by logistic regression, using a manual stepwise technique (backward elimination). The population attributable fractions (PAF) were also calculated as the resulting proportional change in the probability of retirement after a counterfactual exercise where the presence of a RD was artificially eliminated from the sample. In order to calculate indirect costs following early retirement attributable or due to RD, an official national public source (*Quadros do Pessoal* / Personnel Records from the Ministry of Solidarity and Social Security) was used to estimate unit values of production by gender, age-group and region, using the human capital approach, which values healthy time lost due to RD using market wage rates (adjusted for social security contributions). Years of working life lost (YWLL) were estimated as the difference between each participant's current age and the respective retirement age, while the potential years of working life lost (PYWLL) were given by the difference between official and actual retirement ages. The share of time in inactivity was also calculated (Inactivity ratio=YWLL/active age-range). All results were computed as weighted data, in order to take into account the stratified sampling design of the surveys. Statistical analyses were carried out using Stata 12.0.

Finally, a comprehensive review using PubMed, the Cochrane Library and the Portuguese institutional repositories was done to identify and analyse studies either in English or Portuguese published between January 2000 and June 2016 that evaluated the impact of interventions targeting early retirement in RD patients.

RESULTS: In 2005-2006 (INS), 37.2% of the Portuguese population aged 50-64 years self-reported at least one RD and among these 52.6% were not employed, compared with 40.7% of those without RD (p<0.001). 45.1% of the studied population was not employed and more frequently self-reported "poor" to "very poor" health than those employed (31.6% vs. 16.4%, respectively; p<0.001). A larger average number of major chronic diseases *per capita* was also found in those not employed (1.9 vs. 1.4, p<0.001). RD were more prevalent (43.4% vs. 32.1%; p<0.001) and independently associated with early retirement (OR: 1.24; CI: 1.01-1.52) and broad early exit from work (OR: 1.31; CI: 1.12-1.52). The annual indirect costs following premature exit from work attributable to RD were €650 million (€892 per RD patient), while early retirement amounted to €367 million (€504 per RD patient).

In 2011-2013 (EpiReumaPt), 34.2% of the studied population self-reported at least one RD and among these 58% were not employed. 51.6% of the studied population was not employed and 29.9% were retired. Among the early retirees, 43.2% were on grounds of ill-health (12.9% of the overall sample), of which in turn about a third (30.4%) was specifically due to RD. Thus, 13.1% of all retirees and 3.9% of the Portuguese population within the studied age-range self-reported RD as the main reason for early retirement. Those who were employed (48%) had higher levels of education, were less obese and had a lower number of chronic diseases compared with participants out of work, in particular those early retired due to RD. Employed people also have less RD than the early retirees (30.0% vs. 40.2%, respectively; $p<0.001$). In fact, as in 2005-2006 with the INS database, self-reported RD was independently associated with early retirement (OR: 1.37; CI: 1.01-1.84).

The majority of the early retirement due to RD was observed in females (81.6% vs. 41.5% of females in the early retirement group unrelated with RD). The estimated early retirement self-reportedly to be caused by RD is potentially associated with an annual cost of up to €910 million (€555 *per capita*; €1625 per self-reported RD patient and €13,592 per early retiree due to RD). Females contributed with the majority of these costs (€766 million; €882 per female versus €187 per male). We observed a total number of 389,939 accumulated YWLL (228 per 1000 inhabitants) and 684,960 PYWLL (401 per 1000 inhabitants). The mean YWLL and PYWLL inactivity ratios were 12% and 21%, respectively. Participants with higher values of disability, measured by the Health Assessment Questionnaire (HAQ), have the highest risk of early retirement (OR: 1.58; CI: 1.27-1.97). The individuals with RD and highest levels of disability (i.e. HAQ scores ≥ 2) are at the utmost risk of early retirement (55.3% vs. 35.1% for all RD population and 31.9% for those with HAQ scores ≥ 2 but without RD). An almost linear relationship between levels of disability and the probability of early retirement was observed, with its y-intercept and slope being increased by RD, which is consistent with the results obtained with OA.

Still using the EpiReumaPt survey, it was estimated a prevalence of clinically confirmed OA in the studied age-group of 29.7% (men: 16.2% and women: 43.5%. Knee OA: 18.6%; hand: 12.6%; hip: 3.6%). OA was associated with early exit from paid employment, specifically knee OA (OR: 2.25; CI: 1.42-3.59), but not with early retirement *stricto sensu,* since unemployment seems to be a major channel of work

loss for patients with OA. Other OA locations did not have a statistically significant effect on work loss. Early exit from paid employment due to OA led to a total of 143,262 YWLL and 338,822 PYWLL (84 and 198 per 1000 inhabitants in the studied age-group, respectively). The estimated annual indirect cost attributable to OA was €656 million (€384 per capita; €1294 per OA patient and €2095 per OA patient out of work).

Knee OA patients with worst scores on symptoms, pain, quality of life and ability to perform activities of daily living, measured by the Knee injury and Osteoarthritis Outcome Score (KOOS), were more likely to be found out of work. This particularly applies for pain, which seems to play a key role in the risk of workforce withdrawal. A strong association was seen between pain interference and premature work loss, especially within the knee OA population (OR: 1.52; CI: 1.16-1.99).

Concerning the literature revision on possible interventions aiming to reduce early retirement, several published studies testing pharmacologic and non-pharmacologic vocational rehabilitation interventions were identified. None was specifically identified for Portugal. The general low quality of the literature and its inconsistency makes it unfeasible to draw definitive conclusions. However, some broad recommendations were outlined. Despite the lack of good quality evidence on this field, there seems to be a growing interest in the international scientific community with several ongoing promising studies promoting such interventions.

CONCLUSIONS: In Portugal, self-reported RD are associated with early exit from paid work, specifically early retirement. Currently, there is a meaningful number of people who claimed to be retired prematurely due to RD. This translates in many years of working life already lost and many others still potentially to be lost. Indirect costs due to self-reported RD are also substantial, equivalent to at least 0.5% of the Portuguese GDP. By specifically analysing OA, the most prevalent rheumatic disorder, it was possible to verify that the productivity loss due to RD is potentially even higher than the one obtained when analysing self-reported RD as a whole. Regardless the exact magnitude of the estimates, it seems undisputable that the foregone productivity caused by RD is enormous. Due to the lack of good quality data and the inconsistency currently found in the literature, it is difficult to recommend an intervention expected to be inevitably effective. Given the lack of

longitudinal assessments, it is utterly important to promote further research based on long-term cohorts aiming to collect occupational and health information in our country, as well as data on the impact of interventions targeting early retirement caused by rheumatic disorders.

RESUMO

INTRODUÇÃO: As doenças reumáticas (DR) são caracterizadas por dor e redução na amplitude de movimento e função em uma ou mais áreas do sistema músculo-esquelético. As DR são causas importantes de morbilidade e incapacidade em todo o mundo, dando origem a enormes gastos com saúde. As DR também podem conduzir à reforma antecipada, gerando custos indiretos para a sociedade, nomeadamente através da entidade nosológica mais prevalente, a osteoartrose (OA).

OBJETIVOS: Este estudo teve como principais objetivos: 1) Analisar a associação entre DR e reforma antecipada na população Portuguesa; 2) Calcular a perda de produtividade associada à reforma antecipada atribuível às DR em Portugal; e 3) Identificar possíveis intervenções efetivas que visem a reforma antecipada devido às DR.

MÉTODOS: De modo a alcançar os objetivos pretendidos foram utilizados os dados individuais de dois inquéritos nacionais, transversais, de base populacional - o Inquérito Nacional de Saúde (INS), realizado em 2005-2006, e o primeiro estudo epidemiológico de âmbito nacional sobre DR, realizado em 2011-2013 (EpiReumaPt). Ambos os inquéritos tiveram amostras consideradas representativas das regiões de Portugal Continental (Norte, Centro, a região de Lisboa, Alentejo e Algarve) e as regiões autónomas dos Açores e da Madeira. Todos os participantes com idade entre 50 e 64 anos, que se aproximam da idade legal de reforma, foram incluídos na análise (INS: 3762 homens e 4241 mulheres; EpiReumaPt: 1065 homens e 1727 mulheres). A presença de RD foi considerada quando a autodeclarada pelos participantes. Devido à sua elevada prevalência e incapacidade associada, dedicou-se especial atenção à OA, que foi considerada quando o seu diagnóstico era clinicamente confirmado primeiro por um reumatologista numa consulta ao doente e posteriormente validado por outros 3 reumatologistas no estudo EpiReumaPt, de acordo com os critérios de classificação definidos pelo Colégio Americano de Reumatologia (ACR). No que diz respeito à variável dependente principal, utilizou-se uma definição *lato* e *stricto sensu* de perda de emprego prematura, o que permitiu ter em consideração a existência de diferentes

percursos no sentido da reforma antecipada. Além disso, foi analisada a reforma antecipada devido a DR, tal como diretamente relatado pelos participantes do estudo EpiReumaPt. Outras variáveis de interesse, em particular aquelas que potencialmente podem influenciar a reforma antecipada, foram também descritas e analisadas, incluindo aquelas de natureza sociodemográfica, saúde, estilos de vida e fatores socioeconómicos. Os efeitos da DR autodeclarada e da OA sobre a probabilidade de reforma antecipada foram obtidos a nível individual através da regressão logística. A Fração Atribuível na População (PAF) foi também calculada como a variação proporcional resultante na probabilidade de reforma após um exercício contrafatual em que as DR são artificialmente eliminadas da amostra em estudo. Para estimar os custos indiretos recorreu-se à base de dados salariais "Quadros do Pessoal" do Ministério da Solidariedade e Segurança Social, usando-se estimativas dos custos salariais médios por sexo, região e grupos etários para os anos dos inquéritos, utilizando a abordagem do capital humano, que valoriza o tempo perdido devido às DR usando os salários do mercado (ajustados para as contribuições para a segurança social). Os anos de vida laboral perdidos (YWLL) foram estimados como a diferença entre a idade atual de cada participante e a respetiva idade de reforma, enquanto os anos potenciais de vida laboral perdidos (PYWLL) foram obtidos através da diferença entre as idades oficiais e reais de reforma. A percentagem de tempo em inatividade também foi calculada (rácio de inatividade=YWLL/grupo etário de idade ativa). Todos os resultados foram calculados como dados ponderados, de forma a ter em conta o esquema de amostragem estratificada utilizada nos inquéritos. As análises estatísticas foram realizadas utilizando Stata 12.0.

Finalmente, uma revisão abrangente, recorrendo à *PubMed*, à *Cochrane Library* e aos repositórios institucionais portugueses, foi realizada para identificar e analisar estudos em Inglês ou Português publicados entre janeiro de 2000 e junho de 2016, que tenham avaliado o impacto de intervenções que visem a reforma antecipada devido às DR.

RESULTADOS: Em 2005-2006 (INS), 37,2% dos Portugueses com idade compreendida entre os 50 e os 64 anos autodeclararam pelo menos uma DR, dos quais 52,6% não estavam empregados, em comparação com 40,7% daqueles sem qualquer DR (p<0,001). 45,1% da população estudada não tinha um trabalho

remunerado, pelo que este grupo notificou mais frequentemente um estado de saúde “mau” a “muito mau” comparativamente àqueles que tinham trabalho (31,6% vs. 16,4%, respetivamente; p<0,001). Um número médio superior de doenças crónicas principais *per capita* foi observado entre aqueles que estavam fora do mercado de trabalho (1,9 *vs*. 1,4, p<0,001). A presença de DR foi mais prevalente (43,4% vs. 32,1%; p<0,001) e estatisticamente associada à reforma antecipada (OR: 1,24; IC: 1,01-1,52) e à saída precoce do mercado de trabalho (OR: 1,31; IC: 1,12-1,52). Os custos indiretos anuais decorrentes da saída antecipada do trabalho atribuível às DR foram €650 milhões (€892 por doente com DR), enquanto aquelas mais especificamente decorrentes da reforma antecipada ascenderam a €367 milhões (€504 por doente com DR).

Em 2011-2013 (EpiReumaPt), 34,2% dos Portugueses com idade compreendida entre os 50 e os 64 anos autodeclararam pelo menos uma DR, dos quais 58% não estavam empregados. 51,6% da população estudada não tinha qualquer trabalho pago e 29,9% eram reformados. Entre os reformados, 43,2% referiu que a sua reforma antecipada tinha sido devido a doença (12,9% da amostra total), dos quais, cerca de um terço (30,4%) referiram ter sido especificamente devido a DR. Assim, 13,1% de todos os reformados e 3,9% da população Portuguesa na faixa etária estudada referiram a DR como a principal razão para a sua reforma antecipada. Aqueles que estavam empregados (48%) tinham níveis educacionais mais elevados, eram menos obesos e tinham um menor número de doenças crónicas em comparação com os participantes que estavam fora do mercado de trabalho, em especial os reformados antecipadamente devido a DR. Os participantes empregados também apresentaram menos DR que aqueles com reforma antecipada (30,0% vs. 40,2%, respetivamente; p<0,001). Tal como em 2005-2006 no INS, a DR autodeclarada apresentou-se estatisticamente associada com a reforma antecipada (OR: 1,37; IC: 1,01-1,84).

A maior parte da reforma antecipada devido a DR foi observada no sexo feminino (81,6% vs. 41,5% de mulheres no grupo de reforma antecipada não relacionada com DR). A reforma antecipada que de acordo com os participantes do EpiReumaPt foi devida a DR está potencialmente associada a um custo anual que ascende aos €910 milhões (€555 *per capita*; €1625 por doente com DR autodeclarada e € 13.592 por reformado devido a DR). As mulheres contribuíram com a maior parte destes

custos (€766 milhões; €882 por cada mulher versus €187 por cada homem). Observou-se um número total de 389.939 YWLL acumulados (228 por cada 1000 habitantes) e 684.960 PYWLL (401 por 1000 habitantes). Os rácios de inatividade resultantes dos YWLL e PYWLL foram 12% e 21%, respetivamente. Os participantes com maiores valores de incapacidade funcional, medida pelo *Health Assessment Questionnaire* (HAQ), têm maior probabilidade de reforma antecipada (OR: 1,58; IC: 1,27-1,97). Os indivíduos com DR e níveis muito elevados de incapacidade (ou seja, HAQ com pontuações iguais ou superiores a 2) têm maior risco de reforma antecipada (55,3% vs. 35,1% para toda a população DR e 31,9% para aqueles com HAQ ≥ 2, mas sem DR). Foi observada uma relação quase linear entre os níveis de incapacidade e a probabilidade de reforma antecipada, com o declive e interceção no eixo das ordenadas aumentados na presença de DR, algo que é consistente com os resultados obtidos com a OA.

Na base de dados do EpiReumaPt estimou-se uma prevalência de OA clinicamente confirmada de 29,7% na faixa etária estudada (homens: 16,2% e as mulheres: 43,5%. OA do joelho: 18,6%; mão: 12,6%; anca: 3,6%). A OA está associada à saída precoce do mercado de trabalho, mais especificamente a OA do joelho (OR: 2,25; IC: 1,42-3,59. As outras localizações anatómicas com OA não apresentaram qualquer associação), mas não com a reforma antecipada *stricto sensu*, dado que o desemprego parece ser um canal importante de saída antecipada do mercado de trabalho nos doentes com OA. A saída precoce do emprego remunerado devido à OA causou potencialmente um total de 143.262 YWLL e 338.822 PYWLL (84 e 198 por 1000 habitantes na faixa etária estudada, respetivamente). Os custos indiretos anuais atribuíveis a OA ascenderam a €656 milhões (€384 *per capita*; €1294 por cada doente com OA e €2095 por cada doente com OA e fora do mercado de trabalho).

Nos doentes com OA no joelho com piores pontuações nos sintomas, dor, qualidade de vida e capacidade de realizar atividades da vida diária, medida pela escala KOOS (*Knee injury and Osteoarthritis Outcome Score),* tinham maior probabilidade de se encontrarem fora do mercado de trabalho. Isto aplica-se particularmente no caso da dor, que parece desempenhar um papel basilar no risco desta perda de produtividade. Verificou-se uma forte associação entre a interferência da dor em

atividades laborais da vida diária e a saída do mercado de trabalho antecipada, especialmente entre a população com OA do joelho (OR: 1,52; IC: 1,16-1,99).

Relativamente à revisão da literatura sobre possíveis intervenções com o objetivo de reduzir a reforma antecipada devido a DR, foram identificados estudos publicados sobre medidas farmacológicas e não-farmacológicas, pelo que nenhum dizia respeito especificamente a Portugal. A inconsistência encontrada na literatura disponível, bem como a genérica fraca qualidade da evidência, tornam inviáveis quaisquer conclusões definitivas. No entanto, algumas recomendações gerais foram identificadas, pelo que parece existir um interesse crescente na comunidade científica internacional sobre este assunto, algo que é acompanhado por diversos estudos promissores que estão actualmente a decorrer.

CONCLUSÕES: Em Portugal, as DR autodeclaradas estão associadas ao abandono precoce do mercado de trabalho, e mais especificamente à reforma antecipada. Atualmente, há um número expressivo de pessoas que afirmam ter tido reforma antecipada devido a DR. Algo que se traduz em muitos anos de vida laboral já perdidos e muitos outros ainda potencialmente por perder. Os custos indiretos devidos à DR autodeclarada também são substanciais, o equivalente a pelo menos 0,5% do PIB Português. Ao analisar especificamente a OA, a doença reumática mais prevalente em todo o mundo, foi possível verificar que a perda de produtividade devido a DR é potencialmente ainda mais elevada do que aquela obtida quando se analisam as DR autodeclaradas no seu todo. Independentemente da magnitude exata das estimativas, parece indiscutível que a produtividade perdida causada por DR é imensa. Devido à lacuna de evidência com boa qualidade e a inconsistência encontrada atualmente na literatura, é difícil recomendar uma intervenção inevitavelmente efetiva com vista a evitar a reforma antecipada devido às DR. Dada a falta de avaliações longitudinais, é fundamental que a investigação futura se fundamente em coortes de doentes de longo-prazo com o fim de recolher dados sobre saúde e de natureza ocupacional no nosso país, bem como informação sobre o impacto das intervenções que tenham como objetivo evitar a reforma antecipada causada por distúrbios reumáticos.

SCOPE AND CONTEXT

In late 2010, just after finishing my Master of Science in Epidemiology, I was invited by Professor Jaime Branco to join the EpiReumaPt research team. At that time the project was just starting so I had the privilege to make a contribution almost from the very beginning. It allowed me to experience first-hand all steps of a nationwide, large-scale epidemiologic study. Indeed, it was an invaluable opportunity that I shall never forget with a great learning curve with a brilliant team, composed by renowned rheumatologists and led by Professor Jaime Branco and Professor Helena Canhão. In addition to all this, a few months later, I became responsible for setting up and writing the protocol for the CoReumaPt study to follow-up the EpiReumaPt participants. It was a challenge not only from the technical point of view, but also a tough test of informal leadership, as it was not always straightforward to establish consensus among the experts who co-autorship this protocol. After finishing this task and as soon as EpiReumaPt was moving to the field work, I became more focus in pursuing my PhD. I had some ideas, but I wasn't sure if any would meet the standards of a PhD. This is when I came across with another brilliant mind, Professor Miguel Gouveia, who generously gave me the embryonic ideia from where all this research would evolve. Professor Miguel Gouveia also accepted to be my PhD supervisor along with Professor Helena Canhão (and more recently Professor João Eurico da Fonseca, with whom I shared some projects in the past, including my Master's thesis). I believe I couldn't be better served concerning the project and its supervision.

Our first approach was the INS database followed by EpiReumaPt - our steps were synchronized with the EpiReumaPt's phasing. I continuously presented preliminary results of EpiReumaPt in international congresses and also published articles in international, peer-reviewed journals, always carrying in mind the main output of all this work – this thesis and, hopefully, some useful knowledge for the scientific community and for the Portuguese society.

THESIS OUTLINE

This thesis is divided into three sections:

Section A addresses the General Introduction, the Hypotheses and the main and secondary research Objectives. The General Introduction describes the context of the research, providing the etiological model and the theoretical foundation for the thesis. It presents background information on RD, its known burden and epidemiology, and summarizes the current knowledge about its relationship with early retirement and due impact. This Section also contains a brief description of the general methods used during the research and the respective sources of data.

Section B presents three distinct Parts with the results of this thesis, published or submitted to international peer-reviewed journals. ***Part 1*** includes one article, which describes the first approach in this research to explore the relationship between chronic diseases, particularly self-reported RD, and early withdrawal from work. ***Part 2*** comprises three articles that detailed the in-depth findings about the economic impact of early retirement attributable to self-reported RD and, more specifically, to clinically confirmed OA. ***Part 3*** includes one article describing a literature review about the current knowledge of interventions aiming to reduce early retirement due to RD.

Broadly, **Part 1** addresses the causes of early retirement, **Part 2** its consequences, while **Part 3** its possible solutions.

Section C is composed by the General Discussion, the Conclusions and Future Perspectives. The General Discussion complements the Discussion section of each individual article included in the previous Section and aims to build a global picture from the whole research. It also deliberates around the potential limitations of the research and draws attention for possible avenues to study this topic.

SECTION A

GENERAL INTRODUCTION

RHEUMATIC AND MUSCULOSKELETAL DISEASES

Rheumatic diseases (RD), also called musculoskeletal (MSK) diseases, are characterized by pain and a consequent reduction in the range of motion and function in one or more areas of the MSK system; in some diseases there are signs of inflammation: swelling, redness, warmth in the affected areas.[1] RD encompass a wide spectrum of conditions, from those of acute onset and short duration to chronic progressive course disorders including osteoarthritis (OA), rheumatoid arthritis (RA), osteoporosis (OP) and low back pain (LBP). RD have a broad array of clinical manifestations, but are generally characterized by inflammation, damage and/or pain of the joints and connective tissues. Overall, women are more often affected and the incidence increases with age. [2,3]

RD have a profound negative impact on many aspects of a patient's life as well as on the society as a whole.[4] Patients are hampered in their daily activities by pain,[5] physical disability,[6] and fatigue,[7] seriously affecting their quality of life.[5]

RD are leading causes of morbidity and disability throughout the world, giving rise to enormous healthcare expenditures and loss of work.[6,8]

The rheumatic conditions with the greatest impact on society include:

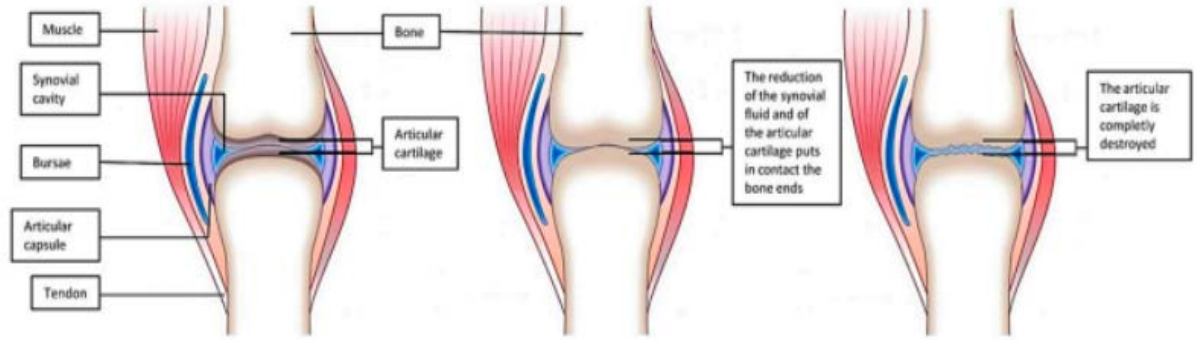
Osteoarthritis:

OA is the most common degenerative joint disorder in the world. It is associated with ageing and affect the joints that have been continually stressed throughout the years including the knees, hips and hands. [9] OA has been designated as one of the key conditions for special attention during the WHO's Bone and Joint Decade (2000-2010).[10]

OA is characterized by inflammation, softening, fibrillation and degradation of articular cartilage, as well as abnormal bone growth in the form of osteophytes. Other anatomical changes involve the appearance of subchondral cysts, abnormal remodelling of subchondral bone, muscle weakness and joint space narrowing

(Figure 1).[11] OA is a leading cause of chronic pain and mobility limitation, particularly in women and older individuals.[12]

Figure 1 - The joints' alterations that occur in OA



Source: Musumeci G et al. 2015[13]

The precise etiology of OA is unknown, however, it is considered by many to be a multi-factorial disease that may be attributable to: 1) systemic factors such as age, gender, hormones, metabolism, genetics and nutritional factors;[11] 2) mechanical factors including previous joint injury, leg misalignment, muscle weakness and obesity.[14] Of the identifiable risk factors, overweight is considered to be the number one modifiable risk factor for the development and progression of knee OA, with one model estimating that approximately a quarter of all cases of total knee arthroplasty for end stage knee OA could be avoided with weight reduction.[15]

From the epidemiological point of view, because of the high percentage of people suffering from this disease and the increase in life expectancy, OA is one of the most significant causes of disability in the world, making the social and economic cost to the healthcare system vast. Ageing of the population is expected to place OA as a leading cause of disability in the coming future.[4,16]

The economic burden of OA is largely attributable to medication, much of which goes toward pain-related agents, and hospitalization costs (comprising nearly half of direct costs).[17] However, indirect costs for OA are also high, largely a result of work-related losses, an area of study which has received insufficient research attention.[18] In fact, although direct and indirect costs attributable to OA are substantial, it seems that productivity related costs are predominant.[19]

Worldwide estimates are that 9.6% of men and 18.0% of women aged ≥60 years have symptomatic OA.[20] Results from a systematic review showed a prevalence of knee OA, from 6.3% in Greece to 68.4% in the UK; in hip, from 0.9% in Greece to 23% in Croatia; in hand from 2% in Greece to 77.1% in Israel.[21,22] The considerable variation in these estimates largely depend on the case definition used (i.e. self-reported, radiographic and symptomatic OA).[21,22]

In Portugal the latest estimates for the prevalence of OA in the adult population are: 12.4% for knee OA (females: 15.8%; males: 8.6%); 8.7% for hand OA (females: 13.8%; males: 3.2%); and 2.9% for hip OA (females: 3.0%; males: 2.9%).[23]

Rheumatoid Arthritis:

RA is a chronic immune mediated inflammatory disease that preferentially affects the joints, leading to cartilage damage and bone erosions. It tends to strike during the most productive years of adulthood, between the ages of 20 and 40, and is a chronic disabling condition, causing pain and deformity.[9] RA patients have an increased risk of being without a paid job compared to well-adjusted reference groups (odds ratios [OR] 1.2 to 3.4).[24,25] Within 10 years on onset, at least 50% of patients in developed countries are unable to hold down a full-time job.[9] This translates to high costs to society and individual stakeholders, including patients/employees, employers, family members/caregivers, and governments.[26] RA prevalence varies between 0.3% and 1% and is more common in women and in developed countries.[6,27,28] In Portugal, it is estimated to be 0.7% (95% CI: 0.5%-0.9%).[23]

Osteoporosis:

OP is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures of the hip, spine and wrist.[9] The most costly result of OP is the hip fracture, which always requires hospitalization. It is estimated that within one year, 20 to 30% of the patients affected by a hip fracture die, 50-60% become disabled and only 30-40% fully recover their previous functional levels.[29] 1.7 million hip fractures occurred worldwide in 1990; this figure is expected to rise to 6 million in 2050.[9] In Portugal there have been 77,083 hip fractures reported between 2000 and 2008, with annual hospital costs of around 52 million euros.[25,30]

Based on measures of bone mineral density in caucasians, OP is present in 15% of those 50–59 years of age, but these figures increase quickly to 70% of those over 80 years of age.[9] The prevalence of OP in the Portuguese adult population is estimated to be 10.2% (95% CI: 9.0%-11.3%).[23]

Low Back Pain:

LBP is a major health and socioeconomic problem in western countries. LBP can be classified as "specific" (suspected pathological cause) or "non-specific" (about 90% of cases) and is usually defined as acute if it lasts less than 3 months or chronic otherwise.[31] LBP interferes with quality of life and work performance and is the most common reason for medical consultations.[32] It constitutes a major public health problem (as classified by the World Health Organization [WHO]) in industrialized societies, affecting a substantial proportion of the working age population and leading to significant productivity losses (e.g. loss of working days).[33]

The occurrence of LBP is associated with age, physical fitness, excess body weight and strength of back and abdominal muscles. Psychological factors associated with occurrence of back pain are anxiety, depression, emotional instability and pain behaviour (e.g. outward display of pain). Occupational factors, such as heavy work, lifting, bending, twisting, pulling and pushing, may also have a relationship with LBP, as do psychological workplace variables, such as job dissatisfaction. Psychosocial aspects of health and work in combination with economic aspects seem to have more impact on work loss than physical aspects of disability and physical requirements of the job. LBP is the most prevalent MSK condition and affects almost everyone at some stage of life.[4,34] In our country, the latest prevalence estimate is 26.4% (95% CI: 23.3%-29.5%).[23]

THE EPIDEMIOLOGY OF RHEUMATIC DISEASES

In several countries epidemiological studies were already performed in order to specifically ascertain their RD epidemiologic profile as a whole,[35,36,37] or for specific forms of RD, such as spondyloarthritis[38,39] and RA.[40,41,42]

In 1981 the International League of Associations for Rheumatology (ILAR) and the WHO together launched the Community Oriented Programme for Control of Rheumatic Diseases (COPCORD) to fill the gap in the lack of epidemiological data

about MSK pain and arthritis in developing countries. COPCORD is a low-cost, low-infrastructure programme based on regional resources, which already provided data for many countries worldwide, including Bangladesh, Brazil, Chili, China, Cuba, Egypt, Guatemala, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Mexico, Pakistan, Peru, Philippines, Thailand, Tunisia and Vietnam.[43,44]

Many other epidemiologic studies had already been put in place around the globe with a diversity of methodological approaches, RD case definition (e.g. self-reported data or clinical diagnosis) and used settings (e.g. community- or clinical-based). Naturally, these studies provided a wide range of prevalence figures and comparisons must be done prudently.

Until recently the epidemiologic studies to determine the frequency, the distribution and the impact of RD in Portugal were limited to small and non-representative samples, resulting in a considerable gap of knowledge around this relevant matter in our country.[45,46,47,48]

However, the development of the National Program Against Rheumatic Diseases (2004-2010) [49] allowed the planning and implementation of the Portuguese Epidemiologic Study of Rheumatic Diseases (EpiReumaPt)[50,51] from September 2011 to December 2013. EpiReumaPt was the first nationwide project studying RD in the Portuguese population, mainly designed to determine the prevalence of RD covered by the abovementioned Governmental Program: hand, knee and hip OA, LBP, RA, OP, fibromyalgia, gout, spondyloarthritis, periarticular disease, systemic lupus erythematosus and polymyalgia rheumatica. EpiReumaPt found that more than half (56%) of the adult Portuguese population suffers from at least one form of RD. Disease-specific prevalence was reportedly similar to that found in other countries, namely Spain.[23,52] As it occurs everywhere else, prevalence was higher in females compared to males (64.1% versus 47.1%, respectively) and increases with age.[23] EpiReumaPt also aimed at assessing the impact of RD in patients' quality of life, pain, function and productivity.[50,51] Further details regarding this study are given below in this thesis (Brief Methodology – Data Sources).

Cohort studies are one of the best ways to assess and understand the course of RD and its impact in relevant outcomes. Thus, to complement information obtained from cross-sectional prevalence studies and randomized clinical trials, various cohorts and registries of RD patients have been established in the last decade (for instance,

the National Data Bank for Rheumatic Diseases [NDB], [53] the Consortium of Rheumatology Researchers of North America [CORRONA][54] and the British Society for Rheumatology Biologics Register [BSRBR][55]). Large prospective cohorts have increasingly contributed to pivotal research in the field of RD, which would have been difficult to obtain elsewhere. Actually, they constitute one of the major sources of clinical research publications and communications in rheumatology.[56] Prospective cohort studies describe the disease course and may record long-term outcomes, such as early retirement. The Portuguese Society of Rheumatology (SPR) already detains a national register (Reuma.pt)[57] for some rheumatic diseases, but only recently, following the EpiReumaPt study, efforts have been made to create a large prospective cohort for the main RD occurring in the Portuguese population, as explained bellow in this thesis.

BURDEN OF RHEUMATIC DISEASES

MSK conditions are the most common cause of severe long-term pain and physical disability, and they affect hundreds of millions of people around the world. The Global Burden of Disease (GBD) Study[58] - an international project ranking the diseases and risk factors that cause death and disability - estimated the burden disability in 188 countries for the years 1990, 2010 and 2013 – analysed RD as well. Throughout the world, the burden from MSK conditions was exceptionally high. All MSK disorders combined caused 21.3% of the total years lived with disability (YLD) globally - second to mental and behavioural problems (23.2%). When taking into account both death and disability, all MSK disorders combined accounted for 6.7% of the total global disability-adjusted life years (DALY), which was the fourth greatest burden on the health of the world's population (third in the developed countries).[59] Out of all the conditions studied, LBP ranked first (highest) for the disability (YLD), and sixth for the overall burden (DALY). ‘Other MSK disorders’ and OA ranked tenth and 13th highest for YLD, respectively.[58]

In addition to this burden of disability as estimated by the aforementioned measures of health, there is a considerable impact on the individual's quality of life suffering from a RD.[60,61,62,63] In these patients, percentages of depressed mood and anxiety may be twice as high as in the general population.[64]

RD can also hamper everyday activities, and people with MSK conditions are less likely to be employed than people in good health. It is estimated that in Europe MSK disorders constitutes around half of all absences due to disease or health condition.[65]

THE ECONOMIC BURDEN OF RHEUMATIC DISEASES

The economic burden caused by RD is tremendous, both via direct and indirect costs.[25] The direct costs reflect the diversion of resources consumed towards the diagnosis, treatment and management of the illness.[66] It includes medical expenditures (inpatient, outpatient, drugs and the extra costs due to the side effects of drugs) and non-medical ones (formal caregiver, travelling and community services). Indirect costs on the other hand, are productivity losses or the illness-related morbidity and mortality that render human resources unavailable for productive uses.[67] Major cost components for the indirect costs include productivity losses of employed patients because of short or long-term work disability (including absenteeism and presenteeism) and early retirement due to the disease.

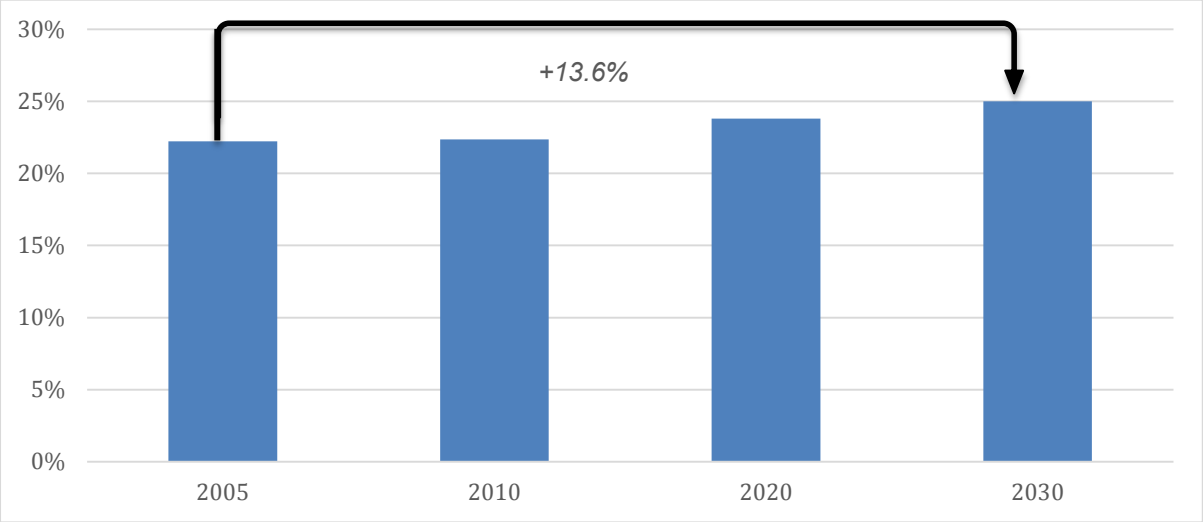
In an *ad hoc* analysis of the European Labour Force Survey, RD accounted for 53% of all work-related diseases in the EU-15. Work-related RD resulted in most lost days and permanent incapacity to work. Overall, they accounted for 50% of all absences from work lasting for more than three days, 49% of all absences lasting two weeks or more and about 60% of all reported cases of permanent incapacity.[68,69] Moreover, some RD patients are reluctant to disclose their condition because they fear discrimination (this was seen in 30% of workers with conditions such as RA),[70] which may lead to increased mental distress as well as presenteeism - workers who go to work when they are ill enough to stay at home.

Studies of the economic impact of RD as a whole have been conducted since the early 1960s using several available data sources.[71] Such studies indicated that the economic impact of RD increased sharply. In US between the years 1996 and 2011, total direct and indirect costs of RD increased by 121%, or nearly four times the rate of increase of the US GDP. As a share of US GDP, total direct and indirect costs for

MSK conditions increased by 67%, from 3.4% to 5.7%. Indirect costs saw an acuter rate of increase of slightly more than 100%. However, in US indirect costs are a smaller share of total costs than direct costs, constituting 0.3% of GDP in 1996 and 0.5% in 2011. Direct costs rose from a 3.2% share to a 5.2% share over the same time period.[72] Other countries have measured the economic impact of RD, such as Canada,[73,74] Australia,[75] the UK,[76] Sweden,[77] and the Netherlands;[78] and contrary to the aforementioned figures for US, some of them came up with a superior relative share of indirect costs, especially when consider arthritis only.[79] In fact, disability and productivity costs can be up to 4 times greater than direct health care costs.[80] This may be partly explained because, as mentioned, MSK complaints are a major cause of work absence due to sickness in developed countries.[4]

In particular, as the most common form of joint disease and a leading cause of disability, OA is associated with an extremely high economic burden.[17,25] This burden is largely attributable to the effects of work disability, comorbid disease, and the expense of treatment. Although typically associated with less *per capita* expenditures than RA, for example, OA translates in overall higher economic burden because of its vast prevalence, which is expected to further escalate (Figure 2), partly a function of the increase in 2 major risk factors: aging and obesity.[17]

Figure 2 – Projected Prevalence of Diagnosed Arthritis in US from 2005 to 2030



Data Source: Bitton R et al. 2009.[17] Based on the US Health Interview Survey.

OA costs seem to increase proportionally with disease severity, for instance a 2009 Spanish study compared costs based on radiographic severity and found that more severe OA patients had higher direct annual costs compared with remaining OA patients.[81] This was consistent with previous research done in Canada by Gupta S *et al*. who found that greater disability, based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, was associated with higher costs in a linear fashion.[82]

DIAGNOSIS AND TREATMENT OF RHEUMATIC DISEASES

The definitive diagnosis of RD must be done by a rheumatologist, by assessing the medical history, performing a physical examination and ordering specific laboratory tests and imaging investigations. RD patients require prompt diagnosis and treatment, as any delay may result in irreversible joint destruction and disability. There is no single medication or treatment which is optimal for everyone. There are treatment options that help manage pain and control arthritis symptoms. Most inflammatory rheumatic diseases are treated with the so-called Disease-Modifying Antirheumatic Drugs (DMARDs), which include also biotechnological drugs, usually called biologics.

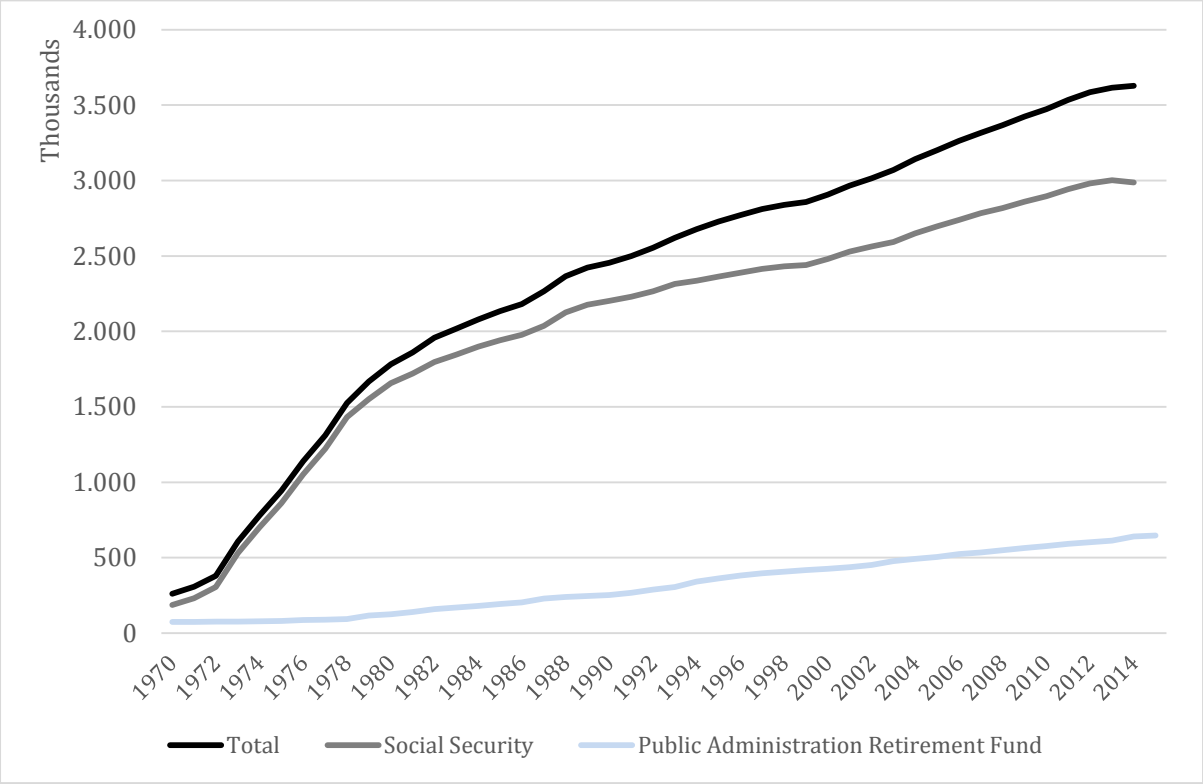
In addition to pharmacologic treatment other methods may play a role in RD management as well: injections into a joint or the soft tissues, physiotherapy and rehabilitation interventions and surgical procedures.[1]

It is crucial to guarantee timely diagnosis and patient access to effective care, aiming to delay or to limit the impact of an established RD. Primary prevention of RD is still beyond our grasp, nonetheless emerging data from natural history studies show that for most RD there is a period of 'preclinical' disease development during which abnormal biomarkers or other processes can be detected and, based on this, perhaps in the near future, it will be possible to implement effective screening and preventive approaches for some RD.[83] Until then, effective postponement of RD progression must be carried out with the most adequate treatments, in order to achieve the best possible clinical and occupational outcomes. In Portugal, despite a clear progression in the last decade, a delay in the access to innovative medications has been observed, mostly due to economic constraints and lack of integration of the different layers across our healthcare system.[84, 85] On this regard, the current expansion of the rheumatology referral network in our National Health Service (NHS)[86] may be a fundamental step to provide the best possible care to RD patients limiting the burden of the disease and reducing early retirement.

EARLY RETIREMENT

Societies are currently facing one of the greatest challenges ever with the increasing population ageing. In Europe, it is estimated that the proportion of people over 65 years of age will triple between 1950 and 2050.[87] Aggravating this economic pressure, in the last decades, most of developed countries faced a declining of the effective age of retirement and the number of retired people has been growing, including in Portugal (Figure 3),[88] which is amongst the countries with the highest generosity of public pensions (e.g. high net replacement rate - defined as the individual net pension entitlement divided by net pre-retirement earnings – 90% versus 71% of the EU28 average and 63% of OECD).[89]

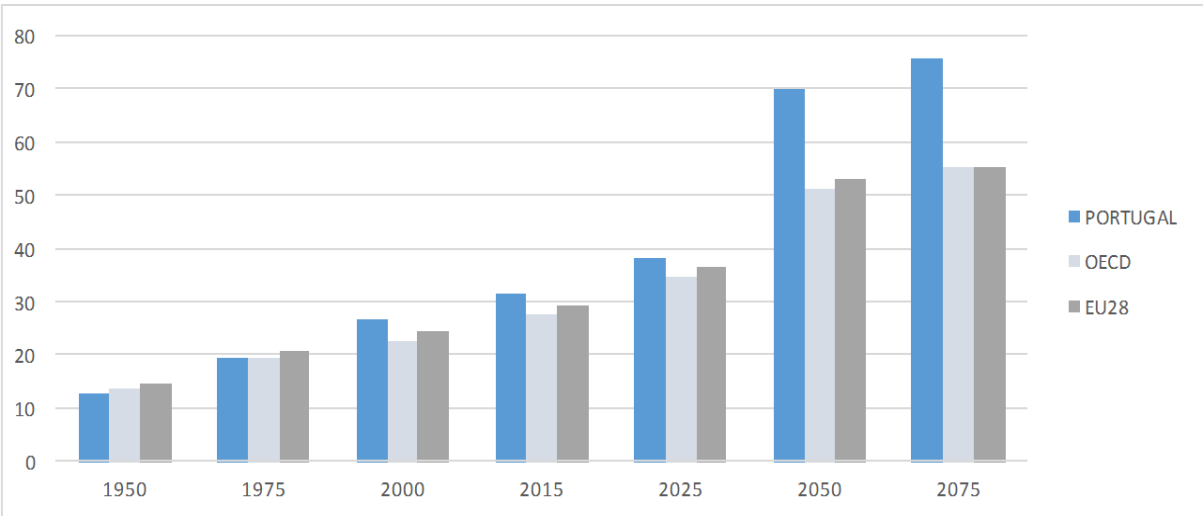
Figure 3 – Evolution on the number of pensions in Portugal



Source: PORDATA; Data Sources: CGA/MTSSS & IGFSS/MTSSS (until 1998) | ISS/MTSSS (as from 1999)

The old-age dependency ratio (i.e. the ratio of the number of elderly persons of an age when they are generally economically inactive to the number of persons of working age) is progressively increasing in Portugal and by 2050 it will double versus 2015 (Figure 4).

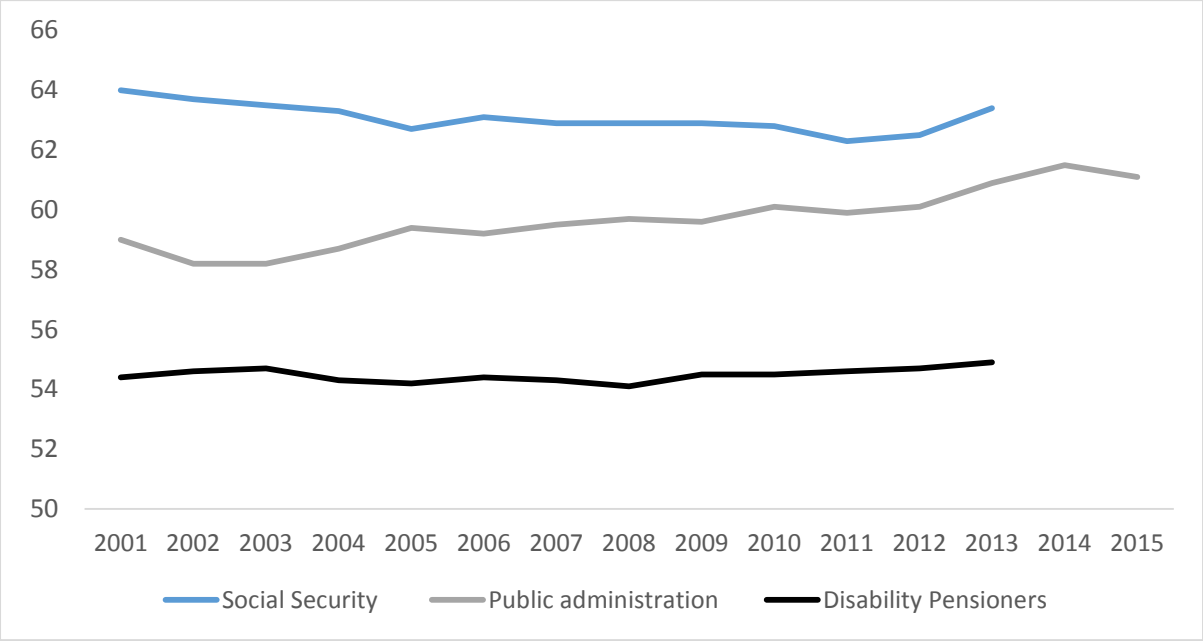
Figure 4 – The evolution of old-age dependency ratio



OECD, Organisation for Economic Co-operation and Development; EU28, European Union comprising 28 member states. The demographic old-age dependency ratio is defined as the number of individuals aged 65 and over per 100 people of working age defined as those aged between 20 and 64.
Source: Pensions at Glance, OECD.[89] Data sources: United Nations, World Population Prospects – 2012 Revision.

As a response to the challenges, politicians in OECD and EU countries have begun to reform their countries' pension systems to induce people to work longer, particularly by reducing financial incentives to retire. In our country, among other alterations, the retirement age was raised from 65 to 66 years and will be linked to changes in life expectancy. The effective old-age mean retirement age was 63.4 for the private sector workers and 60.9 for the public servants in 2013 (Figure 5)

Figure 5 – The evolution of effective retirement age in Portugal



Source: PORDATA; Data Sources: ISS/MTSSS

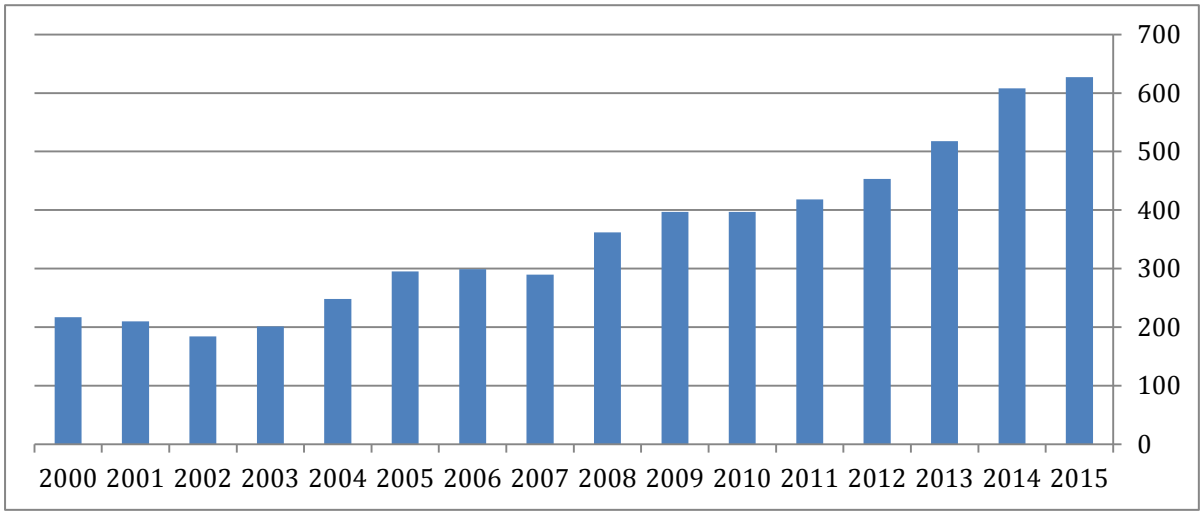
Nowadays, the dissuasion of early retirement is a crucial aim for policymakers. The reversion of the cumulative number of retirees has led to the development of policies to extend the duration of working life, including postponing the retirement age, as it happened recently in Portugal, where the demographic shift has been particularly intensified by persistent low fertility rates. However, isolated measures without taking in consideration the multiple factors, including health status, that affect retirement decisions may be ineffective or even have a long-term deleterious effect on society.

Retirement is a complex process by which individuals withdraw from full-time participation in a job. It is a major transition in peoples' lives, which for some, who sees the opportunity to let go many restrictions and professional harsh conditions, might be a long-awaited life-changing event, while feared by others, who have turned their professional activity into a source of pleasure, personal investment and/or

social acknowledgement.[90,91] Many factors may interfere with retirement decisions. Understanding roots of such decisions might help the individuals to clarify and deal with them and support society to mitigate this highly impactful issue.

All this resulted in a substantial increase in the dedicated research and the number of publications about retirement (Figure 6). Between 2000 and 2015, there was an increase of 75.5% in the growth rate of publications about retirement versus the general growth of all sorts of publications.

Figure 6 – Annual publications with “retirement” in Title and/or Abstract searchable in Pubmed



Data Sources: Pubmed (www.ncbi.nlm.nih.gov/pubmed/)

FACTORS INFLUENCING EARLY RETIREMENT

There is a large literature about potential influencing factors on the retirement decisions. Many of these determinants may be grouped in several categories (Table 1). First, the financial and economic ones, such as the overall economy and the household income; second, the occupational, such as the type of work; third, the sociodemographic factors, such as sex, education and marital status, and lifestyle factors, such as alcohol consumption, smoking, and obesity; and lastly, health-related determinants, such as the self-reported health status and chronic diseases (Table 1).

Table 1 - Potential Determinants of Early Retirement

	Determinants	References
Financial	Economic Environment	92
	Income / Household Income	93 94 95 96 97 98 99 100
	Pension Wealth	93 101
	Saving Habits / Asset Accumulation	102 103
Occupational	Occupational class	97 104 105 106 107 108 109
	High Physical Work Demand	110 111 112 113 114 115 116 117 118
	Work Stress (Demand-Control Imbalance)	96 100 104 111 112 119 120 121
	Work Stress (Effort-Reward Imbalance)	96 100 104 119 120 121
	Job Satisfaction	100 105 110 112 115 122 123 124 125
Sociodemographic	Age	92 93 96 97 98 101 108 109 113 114 119 120 121 124 126 127 128 129 130 131 132
	Gender	96 101 100 106 109 116 118 120 122 126 127 128 129 130 133 134 135 136 137 138 139 140 141 142 143 144
	Education	95 96 97 98 102 109 114 120 121 126 127 129 140 141 143 145
	Marital Status	98 112 126 146
	Partner's Working Status / Couple Decisions	101 124 147 148
	Social Network / Social Support	118 129 133
	Geographic Area (Urban/Rural)	127
	Ethnic Origin	128
Lifestyle	Obesity / Body Mass Index	120 121 126 128 131 134 143 149 150 151
	Exercise / Sedentarism	112 120 126 129 131 150

	Alcohol Consumption	101 120 121 126 152 153
	Smoking	113 118 129 131 153 154
Ill-Health	Comorbidity	97 103 121 126 101 126 127 129 135 137 138 139 155
	Self-Perceived Health Status	98 101 104 105 106 106 112 116 119 120 121 122 124 125 130 135 136 136 140 141 153 155 156 157
	Chronic Pain	107 109 113 131 143 145 156 158
	Mobility	101 121
	Quality of Life (EQ-5D/SF-36)	104
	Rheumatic Diseases	75 108 115 126 127 132 135 136 137 142 143 144 145 152 154 153 155 156 159 160 161 162 163 164 165
	Diabetes	126 137 166 167 168
	Respiratory Diseases	108 126 142 154 155 169 170
	Cancer	97 99 127 135 137 171
	Coronary Heart Disease	108 127 135 136 137 138 142 172 173 174
	Stroke	126 127 135 173 175
	Neurologic Diseases	108 127 176 177 178
	Depression	99 100 101 104 108 114 116 117 126 132 135 136 137 138 139 142 152 153 154 155 179 180 181
	Anxiety	100 108 114 116 132 135 136 137 139 142 143 152 154 158 182
	Other	101 108 113 126 153 155 165 189 179 183 184 185 186 187 188 189

Several studies have found that health status may have a profound impact on the ability of workers to be actively engaged in paid employment and to prolong their meaningful contribution to a productive society. There is evidence from different longitudinal studies that poor health plays a role in exit from paid employment, due to

disability pension,[120,136,155] unemployment[140,155] and official early retirement.[120,136,155] This impact may be detected through broad self-reported health or by studying the presence of specific chronic diseases (Table 1).

It is important to understand that determinants of retirement may present distinct roles depending on the context they operate. Ill-health may have a smaller impact on the hazard of retirement in countries that have strong economic factors taking place. In the past, some authors found that health plays a less important role than the economic variables,[190] whilst others found the opposite.[191] An example of the interplay of determinants of retirement is well depicted in a recent publication that describes some outcomes of the Finnish statutory pension age reform introduced in 2005, which aimed at extending working lives. Contrary to the initial expectations, it seems that offering choice with respect to the timing of retirement may actually encourage healthy workers to choose earlier retirement regardless of the provided economic incentives for continuing in work. The authors concluded that poor health became a weaker predictor of retirement after the statutory pension age reform.[192]

Hence, it is of paramount importance to analyse potential determinants of retirement within the specific setting for which the research is pointing to provide its results.

As it happens with the international literature, it is difficult to reach a final general conclusion about the relationship between health and retirement in Portugal, since few and conflicting results have also been found and published. Uva MS and colleagues have recently summarized the available literature about the relationship between health and retirement, with a particular focus in the Portuguese studies. The authors concluded that, concerning our population, the few studies about health and retirement were focused on different health status indicators, making it difficult to reach a general conclusion (in addition, these studies were primarily looking for the effects of retirement in health). Consequently, the same authors highlighted the need for the establishment of more methodologically valid research studies in Portugal, mainly epidemiologic studies involving the quantification of association and impact measures.[193]

RHEUMATIC DISEASES & EARLY RETIREMENT

RD may play a key role on early retirement because, as explained, usually they are both highly prevalent and disabling. Some studies have analysed the RD effect on early retirement,[10,40,41] but its precise role is inconclusive, reflecting differences on the type of study performed, the setting (with its own labour market and laws regarding work and retirement), the population under study, and the explanatory variables and confounding addressed in the analysis. In 2014, Rogier van Rijn and colleagues performed a systematic literature review on associations between poor health/comorbidities and exit from paid employment through disability pension, unemployment and early retirement. The authors found that most but not all studies were significant when testing RD or MSK complaints with early exit from work.[155] Thus, final conclusions about this relationship are still waiting to be achieved. In addition, most studies of early retirement and health status have been carried out in America, Australia and Northern European countries, but little is known about Southern European countries, such as Portugal.

Bellow, is a summary of some of the most important studies which have addressed the role of RD in early retirement:

- In 2001, Lacaille D and Hogg RS measured the effect of self-reported RD on the working life expectancy of the Canadian population. After analysing cross-sectional data from 58,439 participants (15-65 years) of the 1994 Canadian National Population Health Survey (NPHS) the authors concluded that the working life expectancy of people self-reporting RD is significantly reduced compared to the general Canadian population (4.2 years on average for men and 3.1 for women).[144]
- 2 years later in Denmark, Lund T and Csonka A examined the association between health and work disability (defined as disability pension or long-term sick leave, which has been shown to be associated with transition to disability pension) and found that although the initial univariate analysis confirmed the association between MSK symptoms and work disability, statistical significance was not reached in the multivariate analysis.[154]

- In 2004, Karpansalo M *et al*. by studying the perceived health effect on early retirement in a cohort of 1748 men aged 42 to 60 years from eastern Finland, found that after adjustment for potential confounders those with poor perceived health had a superior risk for disability pensioning, particularly due to chronic illnesses, including MSK disorders.[136]
- In 2007, Solomon C *et al*., collected data on lifetime occupational history, including any health-related job loss, obtained as part of a postal survey of 10,559 men aged 24–70 years old in three rural areas of England and Wales. The authors found that this type of job loss had become increasingly common, especially in relation to RD and mental illness.[108]
- One year later, Schofield DJ and colleagues published a cross-sectional analysis from the Australian Bureau of Statistics 2003 Survey of Disability, Ageing and Carers for people aged 45–64 years. The authors found that, alike other chronic health conditions, arthritis and related disorders, when adjusted for age and sex, were significantly associated with being out of the labour force.[162]
- In the same year, Westhoff G *et al*. described a significant association between morning stiffness and early retirement in German patients with early RA using data from a prospective RA cohort of 916 patients with disease duration ≤24 months.[161]
- Still in 2008, Seyed M. Alavinia & Alex Burdorf, using the Survey of Health, Ageing, and Retirement in Europe (SHARE), studied 11,462 participants who were 50-64 years old. Long-term illnesses, including arthritis and OP, were significantly more common among those persons not having paid employment. However, these authors found a much stronger association with perceived poor health status.[126]
- In 2010, Pit SW and colleagues, analysed which health problems were associated with retirement due to ill-health in Australia. In a cross-sectional analysis of self-reported data of 1993 retired men and 3160 women aged 45-64, OA was significantly associated with this sort of retirement.[135] This finding was later confirmed by the same research team using a larger sample. The analysis of self-reported data of 21,719 women and 16,393 men in the same

age-group showed a significant relationship between OP and OA with early retirement.[137]

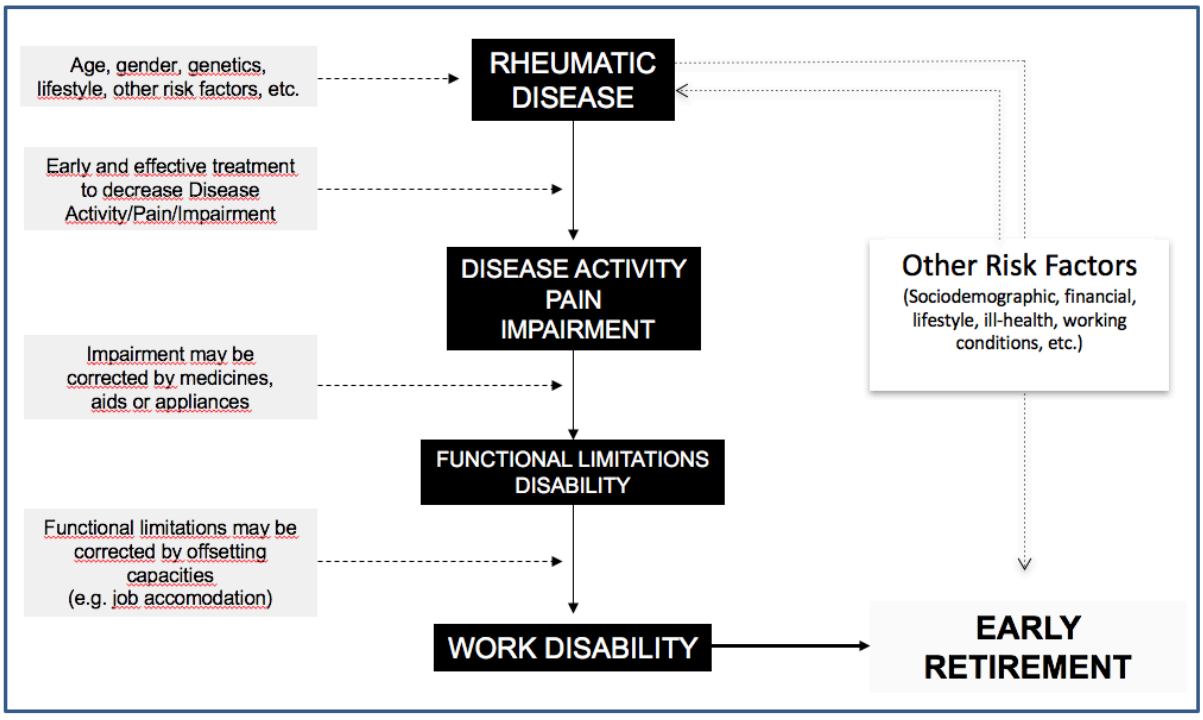
- In 2012, Alexanderson K *et al*., studying a prospective cohort of 20,434 persons employed by the French national gas and electric company, found an elevated risk of disability pension among persons with sick-leave due to MSK disorders.[142] This finding was consistent with a population-based prospective cohort study from Sweden.[164]
- Also in 2012, Jensen LD *et al*. analysed a Danish prospective cohort of nurses' aides and found that general rheumatic complaints predicted disability pension but not voluntary early retirement, while inflammatory RD predicted both forms of work withdrawal.[145]
- In 2013, Ranzi TL *et al*., in one of the few studies in this research area performed in Southern Europe, found a significant association between arthritis and early retirement by using the "Italian Health Interview Survey" with a representative sample of 18,547 people (45-59 years), employed at some time in the past.[127]
- More recently, Leijten FRM *et al*., using self-reported data of employees aged 45–64 years (N=8149) from the Dutch longitudinal Study on Transitions in Employment, Ability and Motivation with 3 years of follow-up (2010–2013), found that RD were associated with disability pensions, early retirement, but not unemployment.[165]

ETIOLOGIC MODEL

Figure 7 depicts the adopted etiologic model that may underlie the connection between RD and early retirement. Throughout the natural history of RD, pain and impairment (e.g. joint inflammation and deformity) usually take place,[1] which in turn may lead to functional limitations (i.e. measures of behaviours that deviate from what is normally expected, in contrast to impairments, which indicate aberrant conditions of tissues, organs, and systems)[194] and disability (i.e. a gap between personal capability and environmental demand),[195, 196] all known predictors of work disability,[113,197, 198,199] meaning that the patient is no longer able to cope with the job requirements. Exit from work and early retirement may then occur if nothing is done to adapt the working conditions to the rheumatic symptomatology and disability. In

each step of this theoretical framework there are influencing factors and some may be changeable to some extent (e.g. pain and disease activity control or job accommodations).

Figure 7 - Etiological model on the relationship between RD and Early Retirement



Adapted from Nagi S[195] and Stattin M[200]

HYPOTHESES

1) Health status might have a significant impact in the early retirement of the Portuguese population.

2) Rheumatic conditions, particularly prevalent forms, such as osteoarthritis, might have a role in this occupational phenomenon.

3) Substantial indirect costs to society are expected to follow early retirement attributable to rheumatic conditions.

4) Interventions aiming to control early retirement due to RD might be effective in reducing this productivity loss.

OBJECTIVES

The main objectives of this study were the following:

1) To examine the association between RD and early retirement in the Portuguese population.

2) To measure the productivity loss associated with early retirement attributable to RD in Portugal.

3) To review possible effective interventions targeting early retirement due to RD.

The secondary objectives of this research were the following:

1) To characterize early retirees in Portugal, according to sociodemographic characteristics, lifestyle factors, health status (e.g. self-reported RD) and other possible determinants of early retirement.

2) To characterize the Portuguese population with self-reported RD and clinically confirmed OA, namely regarding employment status.

3) To identify relevant determinants of early exit from paid employment in Portugal and according with different exit pathways (i.e. retirement, unemployment, other forms of early exit from work).

4) To assess how the association between RD with early retirement is influenced by other relevant factors.

5) To analyse the evolution of this relationship in 2 time periods (2005/2006 versus 2011/2013), by using distinct databases (INS and EpiReumaPt).

6) To measure the productivity loss attributable to self-reported RD and clinically confirmed OA through different retirement routes.

7) To calculate indirect costs attributable to self-reported RD and clinically confirmed OA by different subgroups, according to age, gender and region.

STRUCTURE

The research work was divided in 3 main parts according to its main objectives:

PART 1 - CAUSES OF EARLY RETIREMENT

The Association between Rheumatic Diseases and Early Retirement

PART 2 - CONSEQUENCES OF EARLY RETIREMENT

The Indirect Costs of Early Retirement Attributable to Rheumatic Diseases

PART 3 – SOLUTIONS FOR EARLY RETIREMENT

Interventions to Avoid Early Retirement Attributable to Rheumatic Diseases

BRIEF METHODOLOGY

In Section B, each article includes a detailed description of its methodology. However, below we summarize some of the most important features regarding data source, study population, inclusion and exclusion criteria, case definitions, variables of interest and statistical analysis.

DATA SOURCES

INS:

The 4th Portuguese National Health Survey (INS) was conducted in 2005 and 2006 in all regions of Portugal. The methodology of the INS has been detailed elsewhere.[201,202] Briefly, the sampling frame was built on census data and included all subjects living in individual housing during that period (collective housing such as hospitals, prisons, military barracks, or retirement houses was excluded). The sample was considered representative of the main regions of mainland Portugal (North, Center, Lisbon region, Alentejo, and Algarve) and the autonomous regions of the Azores and Madeira. The primary sampling unit (PSU) was the housing unit, which were then randomly selected within each geographically defined unit. Subjects living in the PSU were then surveyed. Data were collected using face-to-face interviews by trained staff and the questionnaire included self-reported information about perceived health, chronic diseases, lifestyle, social and demographic conditions.

For the purposes of this study, a subsample of all INS surveyed people approaching the statutory pension age, between 50 and 64 years old, was analysed. The sample under analysis was composed of 3,762 men and 4,241 women.

EpiReumaPt:

EpiReumaPt was the first national, cross-sectional, population-based study on RD in all regions of Portugal. The methodology of EpiReumaPt has been detailed elsewhere.[203] Briefly, it was performed among a randomized and representative sample of the adult Portuguese population, recruited between September 2011 and December 2013. Participants were selected through a process of multi-stage random

sampling. The sample was stratified according to the Portuguese Nomenclature of Territorial Units for Statistics (NUTS II; seven territorial units: North, Center, Lisbon region, Alentejo, Algarve, Madeira and Azores) and the size of the population (<2000; 2000–9999; 10,000–19,999; 20,000–99,999; and ≥100,000 inhabitants). Household units were then selected using a random route process. The adults with permanent residence in the selected household with the most recently completed birthday were recruited (one adult per household).[203]

EpiReumaPt had a three-stage approach (Figure 8):

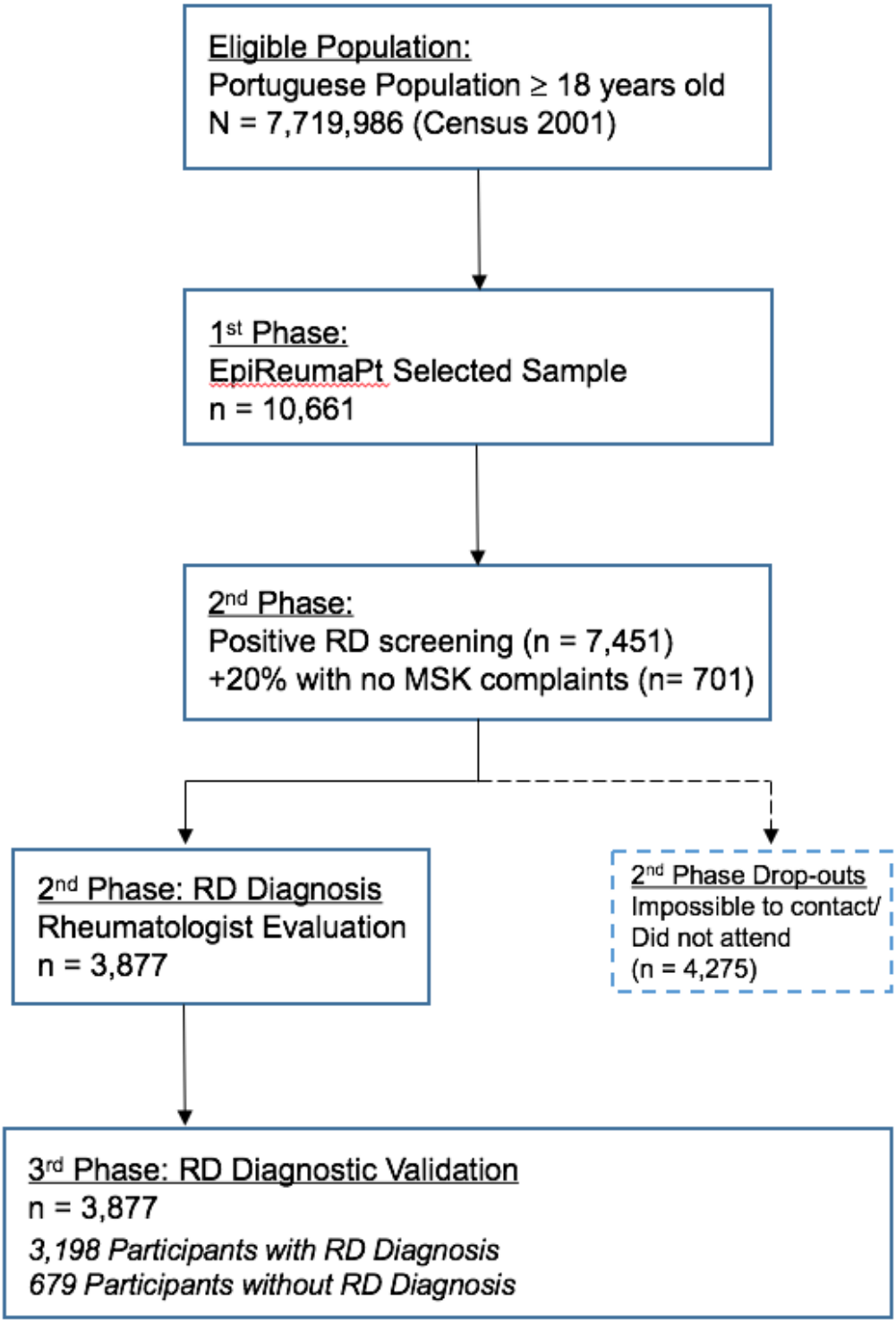
1st Phase) 10,661 adult participants were randomly selected. Trained interviewers undertook structured face-to-face questionnaires that included screening for RD and assessments regarding sociodemographic data, socioeconomic profile, lifestyle, anthropometric data, quality of life, functional capacity and self-reported chronic non-communicable diseases, including RD. Additionally, this phase collected data on the economic impact of RD, such as healthcare consumption, early retirement, disability pensions and unemployment.

2nd Phase) A rheumatologist visit was performed to all participants that were screened positive for at least one RD during the 1st phase, as well as to 20% randomly selected individuals with no rheumatic complaints. Procedures included a standardized physical examination and appropriate laboratory and imaging tests in order to ascertain the RD diagnosis. RD-specific data was also collected in this phase, such as the Knee injury and Osteoarthritis Outcome Score (KOOS)[204]

3rd Phase) Three rheumatologists revised all the information and confirmed the diagnoses according to validated criteria.

For the purposes of this study, a subsample of all EpiReumaPt surveyed people approaching the statutory pension age, between 50 and 64 years old, was analysed. The sample under analysis was composed of 1,065 men and 1,727 women.

Figure 8- Flowchart of the EpiReumaPt Study.



Adapted from Branco JC et al[23]

STUDY POPULATION & ELIGIBILITY CRITERIA

In this study we analysed all non-institutionalized INS/EpiReumaPt participants aged 50 to 64 years old. Details about the inclusion and exclusion criteria used in INS and EpiReumaPt can be found elsewhere.[201,202,203] Thus, apart the aforementioned age restriction, this study did not have any additional eligibility criteria.

CASE DEFINITIONS

Exposure Variable:

The presence of RD was considered for all those participants from the INS or from the EpiReumaPt (1st Phase) who answered positively to the following questions:

INS: "Do you have or did you have any RD (e.g. OA, tendinitis)?"
EpiReumaPt: "Has a doctor ever told you that you have a RD?"

Regarding the case definition of clinically confirmed OA, it was done following the initial diagnosis done by a rheumatologist (2nd Phase of EpiReumaPt) following the validation performed by 3 experienced rheumatologists (3rd Phase of EpiReumaPt), according with the ACR classification criteria, of at least one type of OA: knee OA,[205] hip OA,[206] and hand OA.[207]

Dependent Variable:

The primary outcome of interest in this study was early retirement. We adopted a *lato* and *stricto sensu* definition of early job loss, because there are different channels of exit from the labour market and entry into early retirement, including unemployment, disability pensions and retirement. These pathways are related to the same economic behaviour, which implies an exit from the labour market in the later stages of working life and subsequent loss of productivity for society. Consequently, since the overall negative social and economic impact of early retirement is similar regardless the channels which gave rise to each individual's form of exit from paid work, it was considered also adequate to contemplate a more inclusive outcome in the research. Additionally, these forms of early exit from work pave the way to definitive premature retirement. Thus, exit from paid employment was assumed for all those who didn't report any kind of paid work (part- or full-time).

As opposed, all those reporting any form of paid work were considered employed. This definition was used elsewhere in previous research[101,126] and could be obtained in both datasets (i.e. INS and EpiReumaPt) in a straightforward manner, since details about the employment status were directly asked to all participants of these surveys.

However, we also considered relevant to separately analyse more specific types of exit from work, including early retirement (*stricto sensu)*.[i]

In addition, we analysed the important outcome of early retirement due to RD, which was directly assessed in the EpiReumaPt questionnaire with the following questions:

"What is your current employment situation?" *(dropdown list of different options: Full-time employee; Part-time employee; Housekeeper; Unemployed; work disability; Student; and Retired)* → *(if retired)* "Are you retired due to illness?" → *(if yes)* "Was it due to a RD?"

VARIABLES OF INTEREST

Table 2 lists all variables that were retrieved from INS and EpiReumaPt databases in order to achieve the proposed study objectives.

STATISTICAL ANALYSIS

Each article presented in Section B describes the respective statistical analysis, namely regarding the descriptive analysis,[ii] the multivariable regressions and the calculation of PAF and indirect costs. Of note, some interactions were studied (e.g. RD/OA and age), but did not reach significance in the final models.

The logistic regression models were tested using Linktest (Appendix 1). The assumptions of homoscedasticity, normality, and independence (e.g. no auto-

[i] According to the Portuguese Law, the transition from unemployment to early retirement can occur under pre-specified conditions. This study didn't discriminate between short- and long-term unemployment, given the cross-sectional nature of the surveys (i.e. right censorship) and because short-term unemployment (<12 months) represented just a small share of all registered unemployment within the studied age-group (e.g. in EpiReumaPt less than 1%).

In Portugal, disability pensions are calculated on the basis of a disability percentage, determined by the difference between what an individual can theoretically earn with his or her maintained functional abilities and what he or she earned prior to the disability or what a comparable person without any disability earns.

ii Significance of the study variables was tested using Student's t-test or the Chi-square test, where appropriate. A two-tailed p value of <0.05 was considered to be statistically significant.

correlation) are not needed for the survey mode used in all the analyses, which bases its inference on the sample design (stratification and variation between PSU) and is robust to violations of those assumptions. In other words, there is no need to test for those violations. The basic test of fit is the linktest[iii]. The idea behind the linktest is that if the model is properly specified, one should not be able to find any additional predictors that are statistically significant except by chance. After the logistic regression command, linktest uses the linear predicted value (_hat) and linear predicted value squared (_hatsq) as the predictors to rebuild the model. The variable _hat should be a statistically significant predictor, since it is the predicted value from the model. This will be the case unless the model is completely misspecified. On the other hand, if the model is properly specified, variable _hatsq shouldn't have much predictive power except by chance. Therefore, if _hatsq is significant, then the linktest is significant. This usually means that either we have omitted relevant variable(s) or our link function is not correctly specified (Appendix 1).

INS and EpiReumaPt were designed to obtain representative samples of the Portuguese population. In order to guarantee representativeness, the design effect of both surveys needed to be taken into account in all statistical analysis. This can be achieved by using weighted proportions that have, for this matter, been computed. Specifically for the EpiReumaPt main sample, the initial extrapolation weights were calculated as the inverse of the inclusion probabilities, taking into account the sampling design (i.e. a stratified two-stage cluster sampling design). The stratification was based on the seven NUTS II regions and on five classes of the number of inhabitants per locality (<2,000; 2,000-9,999; 10,000-19,999; 20,000-99,999; >99,999). In each stratum, the first sampling stage consisted in the selection of localities with a probability proportional to its size (number inhabitants aged 18 years old or more), except for localities where the number of inhabitants was larger than 20,000, where all the localities were selected. In the second stage, households were selected using a pseudo-random selection procedure equivalent to the equal probability selection. These weights were submitted to a calibration process by crossing region (seven classes), size of locality (five classes), gender (two classes) and seven age categories (18-25, 26-35, 36-45, 46-55, 56-65, 66-75 and ≥76 years

iii This test is specific from the Stata Statistical Software.

old). This procedure was used to reproduce the known population totals for the crossing margins of these four variables. More details about these weighted proportions may be found elsewhere.[208,203]

All analyses were performed using Stata IC version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Table 2 – Variables of interest retrieved from INS and EpiReumaPt

	Variables of Interest	INS	EpiReumaPt
Sociodemographic	Age	x	x
	Gender	x	x
	Area of Residence (Regions)	x	x
	Marital Status	x	x
Socioeconomic	Educational level	x	x
	Household Income	x	x
Lifestyle	BMI	x	x
	Smoking Status	x	x
	Alcohol Consumption	x	x
Ill-Health	Self-reported Health Status	x	-
	Self-reported chronic diseases	x	x
	Comorbidity Score	x	x
RD	Self-Reported RD	x	x
	Clinically Confirmed OA	-	x
Quality of Life	EQ-5D	-	x
	SF-36	-	x
Pain & Functional Capacity	Chronic Pain	x	x
	Bodily Pain Index from SF-36	-	x
	Longstanding MSK pain	-	x
	Pain Interference	-	x
	HAQ	-	x
	KOOS	-	x
Occupational	Employment Status	x	x
	Early Retirement due to RD	-	x

	Early Retirement	x	x
	Unemployment	x	x
	Disability Pensions	x	x
	Exit from Paid Employment	x	x
	Type of Work	x	-

SECTION B

RESULTS[iv]

All results presented in this Section were published or submitted in international, peer-reviewed journals indexed in PubMed.

PART 1: CAUSES OF EARLY RETIREMENT

The Association between Rheumatic Diseases and Early Retirement

Article A:

Association of rheumatic diseases with early exit from paid employment in Portugal

Pedro A. Laires, Miguel Gouveia

Rheumatology International Vol 34(4):491-501, 2014

Main Characteristics:

Study Population*: 3,762 men and 4,241 women (50-64) who participated in the Portuguese National Health Survey (INS)*

Year: *2005-2006*

Exposure Variable*: Self-reported RD*

Main Outcome*: Early Exit From Work*

[iv] *In all articles, Pedro Laires had the principal role of conceiving and designing the respective studies. Also, data collection, statistical analysis, interpretation of results and drafting of due manuscripts were all tasks led by this author.*

PART 2: CONSEQUENCES OF EARLY RETIREMENT

The Indirect Costs of Early Retirement Attributable to Rheumatic Diseases

Article B:

Indirect Costs Associated with Early Exit from Work Attributable to Rheumatic Diseases

Pedro A. Laires, Helena Canhão, Miguel Gouveia

European Journal of Public Health. Vol 25(4):677-82, 2015

Main Characteristics:

Study Population*: 3,762 men and 4,241 women (50-64) who participated in the Portuguese National Health Survey (INS)*

Year: *2005-2006*

Exposure Variable*: Self-reported RD*

Main Outcome*: Indirect Costs attributable to Early Exit From Work*

Article C:

The Economic Impact of Early Retirement Caused by Rheumatic Diseases - Results from a Nationwide Epidemiologic Study

Pedro A. Laires, Miguel Gouveia, Helena Canhão, Jaime C. Branco

Public Health. 2016 Aug 12. pii: S0033-3506(16)30162-7.

Main Characteristics:

Study Population*: 1,065 men and 1,727 women (50-64) who participated in the EpiReumaPt study*

Year: *2011-2013*

Exposure Variable*: Self-reported RD*

Main Outcome*: Indirect Costs due to Early Retirement*

Article D:

Early Exit From Work Attributable to Osteoarthritis and its Economic Burden

Pedro A. Laires, Helena Canhão, Ana Rodrigues, Mónica Eusébio, Miguel Gouveia, Jaime C. Branco

Ago 2016 (submitted)

Main Characteristics:

Study Population*: 1,065 men and 1,727 women (50-64) who participated in the EpiReumaPt study*

Year: *2011-2013*

Exposure Variable*: Clinically confirmed OA*

Main Outcome*: Indirect Costs attributable to Early Exit from Work*

PART 3 – SOLUTIONS FOR EARLY RETIREMENT

Interventions to Avoid Early Retirement Attributable to Rheumatic Diseases

Article E:

Interventions aimed at Preventing Early Retirement due to Rheumatic Diseases

Pedro A. Laires, Miguel Gouveia, Helena Canhão

Jun 2016 (submitted)

ARTICLES

PART 1 - THE ASSOCIATION BETWEEN RHEUMATIC DISEASES AND EARLY RETIREMENT

Article A: Association of rheumatic diseases with early exit from paid employment in Portugal

Pedro A. Laires & Miguel Gouveia

Rheumatology International. Vol 34(4):491-501, 2014

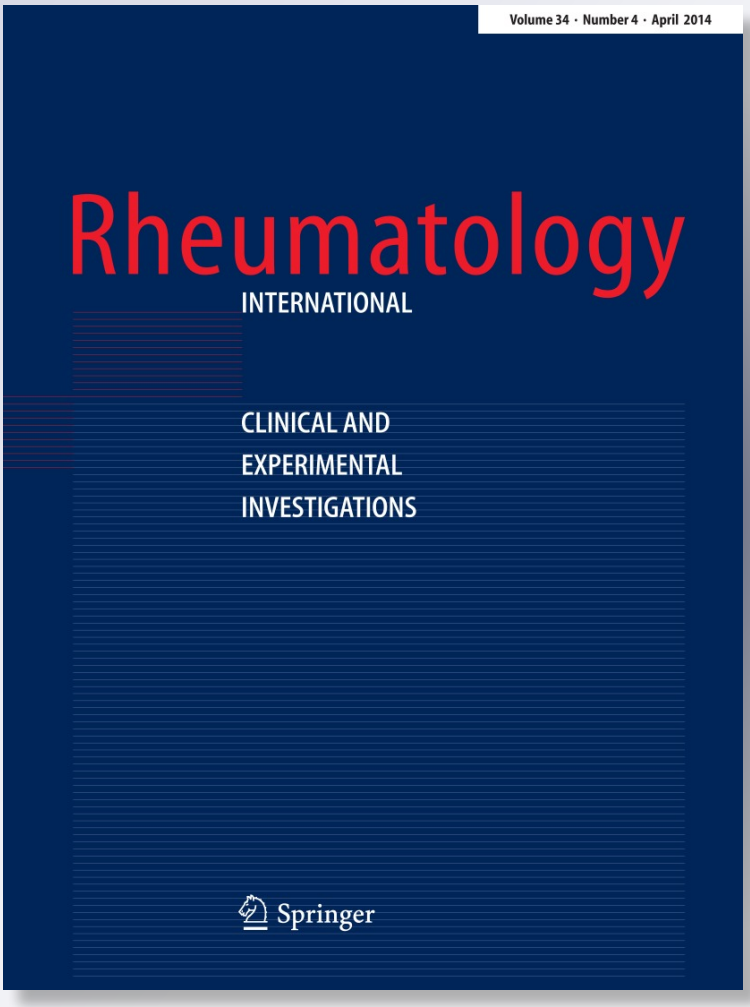
Association of rheumatic diseases with early exit from paid employment in Portugal

Pedro A. Laires & Miguel Gouveia

Rheumatology International
Clinical and Experimental Investigations

ISSN 0172-8172
Volume 34
Number 4

Rheumatol Int (2014) 34:491-502
DOI 10.1007/s00296-014-2948-8



Springer

Rheumatol Int (2014) 34:491–502
DOI 10.1007/s00296-014-2948-8

ORIGINAL ARTICLE

Association of rheumatic diseases with early exit from paid employment in Portugal

Pedro A. Laires · Miguel Gouveia

Received: 18 October 2013 / Accepted: 15 January 2014 / Published online: 31 January 2014

Abstract To examine the association between rheumatic diseases (RD) and other chronic morbidity with early exit from paid employment in the Portuguese population. The study population consisted of all people between 50 and 64 years of age (3,762 men and 4,241 women) who participated in the Portuguese National Health Survey, conducted in 2005/2006. Data were collected on demographics, ill-health, lifestyle, and socioeconomic factors. Logistic regression was used to estimate the isolated effect of rheumatic diseases and other chronic diseases on the likelihood of exit from paid employment. At the time of the survey, 45.1 % of the Portuguese population with ages between 50 and 64 years old were not employed. In the nonemployed population, 31.6 % self-reported "poor" to "very poor" health, whereas 16.4 % did so in the employed population. A larger average number of major chronic diseases per capita were also found in those not employed (1.9 vs. 1.4, $p < 0.001$). In the multivariate models, chronic diseases were associated with early exit from paid employment. In particular, rheumatic diseases were more prevalent (43.4 vs. 32.1 %) and associated with early exit from work (OR 1.31; CI 1.12–1.52, $p = 0.001$). This study suggests an association between RD and other major chronic diseases with early exit from paid employment in Portugal. Thus, health and social protection policies should target these chronic disorders in order to better address sustainability issues and social protection effectiveness.

Keywords Rheumatic diseases · Musculoskeletal disorders · Chronic diseases · Chronic morbidity · Early retirement · Exit from paid work · National health surveys

P. A. Laires (✉)
Sociedade Portuguesa de Reumatologia (Portuguese Society of Rheumatology), Av. de Berlim, 33 B, 1800-033 Lisbon, Portugal
e-mail: laires.pedro@gmail.com

M. Gouveia
Catolica Lisbon School of Business and Economics, Lisbon, Portugal

Introduction

Europe has observed an outstanding increase in life expectancy, while at the same time rates of labor force participation among older people have been decreasing [1]. Older workers are leaving the labor market in great numbers [2], and early exit from employment provides a major challenge to social and health policies. Portugal is already among the oldest countries in the world, with one of the highest old-age dependency ratio, and is currently facing a shrinking number of economically active people supporting a growing economically dependent elderly population [3]. Thus, this trend is hardly feasible and early exit from paid employment in Portugal generates a serious problem for social and economic sustainability. In fact, it might just be at the very forefront of a general European concern with premature exit from work of its potential labor force. Identification of relevant determinants of early exit from paid employment is clearly a prerequisite to delineate strategies and interventions aiming to shift from early exit to the virtuous cycle of active aging [2].

There is a large literature on this issue and it is possible to identify some variables that might explain the retirement decision. First, the financial incentives, such as disability pensions or household income [4–6]; second, the type of work [7–9]; third, the sociodemographic factors, such as sex, education and marital status [10], and lifestyle factors,

such as alcohol consumption [11], smoking [12], and obesity [13–15]; and lastly, health-related determinants, such as comorbid conditions [2, 10, 11, 16–24]. These main types of determinants may interact. For instance, health shocks may have a smaller impact on the hazard of retirement in countries that have the strongest financial incentives to retire early [25]. On the other hand, countries with relatively more generous pension schemes due to disability, such as the case of Portugal and other southern European countries [26, 27], are expected to suffer more impact from ill-health on the hazard into early retirement [26]. Furthermore, although the effect of health status on early retirement has long been recognized, that effect is not always straightforward due to this interdependence with other types of determinants. For instance, chronic diseases such as rheumatic diseases (RD) may play a key role on early retirement because usually they are both highly prevalent and disabling, affecting daily functioning [28, 29], which is particularly relevant for occupations where working conditions cannot be modified or adjusted to a reduced work ability of employees [7, 30, 31]. In fact, studies have already shown that the presence of chronic disorders is indeed associated with a premature departure from labor market [10, 32, 33]. However, some other studies have suggested that employees with chronic disorders tend to retire later because they likely have accumulated fewer assets during their working life [20]. Hence, the role and the magnitude of the effect of ill-health in early retirement is far from being the same across all contexts.

A lot remains to be understood about the relationship between ill-health and early retirement and the possible influence of the social context and other factors on this relationship. Moreover, since health status encompasses a broad array of underlying clinical conditions, it is also of interest to assess how specific symptoms and chronic conditions are affecting workers' withdrawal from the workforce. Previous research has suggested associations of exit from work with diseases like cancer [34], heart disease [35], depression [36], disorders of the nervous system [37, 38], and others [10, 11, 39]. The association with RD is particularly interesting. These diseases are highly prevalent in the western world, and their clinical and functional impacts may be profound, representing major causes of disability among workers, particularly on manual workers, who are exposed on average to harsher working conditions. Some studies have analyzed the RD effect on early retirement [10, 40, 41], but again its isolated role is inconclusive, reflecting differences on the type of study performed, the population under study, and the explanatory variables included in the analysis. Final conclusions about this relationship are therefore still beyond our grasp. Besides, most studies of early retirement and health status have been carried out in the United States and Northern European countries, but little is known about Southern European countries, where disability due to RD and other chronic diseases may represent a quantitatively relevant reason for exit from the labor market.

Main aims of this study are as follows: (a) To examine the association between RD and other major chronic diseases with exit from paid employment in the Portuguese population approaching the statutory retirement age and (b) To assess how this association is affected by other factors (including personal, financial, socioeconomic, and working conditions).

Methods

Sample

The source of data for this study was the 4th Portuguese National Health Survey (INS), which was conducted in 2005 and 2006 in all regions of Portugal. The methodology of the INS has been detailed elsewhere [42, 43]. Briefly, the sampling frame was built on census data and included all subjects living in individual housing during that period (collective housing such as hospitals, prisons, military barracks, or retirement houses was excluded). The sample was considered representative of the main regions of mainland Portugal (North, Center, Lisbon region, Alentejo, and Algarve) and the autonomous regions of the Azores and Madeira. The primary sampling unit (PSU) was the housing unit and sampling built on the population and housing census. Within each main region, two strata were defined: the *freguesias* (corresponding to townships) and, within the *freguesias*, geographically defined units of 240 lodgings. The PSUs were then randomly selected within each geographically defined unit. Subjects living in the sampling unit were then surveyed. The participation rate (defined as the percentage of households who responded) as reported by the National Institute of Statistics was 76 % [42, 43]. Data were collected using face-to-face interviews by trained staff and the questionnaire included self-reported information about perceived health, chronic diseases, lifestyle, social, and demographic conditions.

For the purposes of this study, a subsample of all INS surveyed people approaching the statutory pension age, between 50 and 64 years old, was analyzed. The sample under analysis was composed of 3,762 men and 4,241 women.

Measures

Early retirement was considered as being out of paid work before age 65, which is the statutory retirement age in Portugal. Thus, a broader definition of early retirement (i.e.,

exit from paid employment) was adopted. There are different channels of exit from the labor market and entry into early retirement, including unemployment, disability, and pure early retirement [5, 44–47]. A caveat of this approach is that it doesn't differentiate temporary (e.g., transitory unemployment) from definitive exit from labor market (e.g., official retirement); however, adopting a broader definition of early retirement enabled this research to take into account the existence of different pathways to retirement. These pathways are related to the same economic behavior, which implies an exit from the labor market in the later stages of working life and subsequent loss of productivity for society. Consequently, since the overall negative social and economic impact of early retirement is similar without regard of the channels which gave rise to each individual's form of exit from paid work, it was considered more adequate to consider this more inclusive outcome in the research. Additionally, temporary forms of early exit from work pave the way to definitive premature retirement, which highlights the need for the identification of determinants and possible interventions that might adjourn definitive decision of early retirement. Thus, exit from paid employment was considered for all those who didn't report any kind of paid work. As opposed, all those reporting any form of paid work were considered employed. This definition was used elsewhere in previous research [11, 48].

Health measurement

The presence of major comorbidities was assessed through self-reporting of the following clinical disorders: RD, chronic pain, diabetes, hypertension, asthma, cancer, renal impairment, respiratory diseases (chronic obstructive pulmonary disease and chronic bronchitis), previous stroke, previous myocardial infarction (MI), anxiety, and depression. A proxy measure of general morbidity was built as the sum score of all aforementioned chronic illnesses (comorbidity score).

The European version of self-perceived health, a 5-point scale questionnaire with answers ranging from "very good" to "very poor", was used to define perceived health status. This questionnaire is a broad indicator of health-related well-being [49, 50] and has been shown to be a good indicator of general physical and mental health [16, 51, 52]. Thus, respondents were asked to describe their general health as "very good," "good," "fair," "poor," or "very poor." For this analysis, the variable was transformed into 3 major categories ("very good"/"good", "fair", and "poor"/"very poor").

Lifestyle factors

Smoking status was classified into 3 categories (Not a smoker/occasional smoker; Ex-smoker; current smoker), alcohol consumption was transformed in a dichotomous variable (no/yes) for daily alcohol consumption, and obesity measured according to the body mass index (less than 25 m^2/kg; between 25 and 30 m^2/kg; and 30 m^2/kg or more).

Sociodemographic variables and working type

Area of residence was defined according to the regional location of each household (North; Center; Lisbon region; Alentejo; Algarve; Azores; and Madeira). Age was grouped into 3 age ranges with 5-year intervals (50–54; 55–59; 60–64 years old). Marital status variable was grouped into 4 categories (single; married; divorced; widowed). Regarding socioeconomic characteristics, educational level was classified into 3 major levels according to the highest qualification completed: low (no education/primary school), medium (basic school between primary and secondary levels), high (secondary education/university degree), monthly income of each household was distributed in 4 categories (€500 or less; €500–€900; €900–€2000; €2000 or more), and occupational social class, which refers to the respondent's current occupation or last occupation, was assigned according to a simplified version of the UK Registrar General's Classification of occupations, already used in previous similar research [49]. The six original social classes were collapsed into two broad categories: nonmanual workers and manual workers.

Statistical analysis

Descriptive analysis was performed to compare exit from paid employment against a population with paid employment. Prevalence of retirement and other characteristics were computed as weighted proportions, in order to take into account the sampling design of the survey. The association of early exit from paid employment with health variables was assessed through logistic regression analysis. The first step in the analysis was to establish cross-sectional univariate associations between exit from paid employment and health measures, sociodemographic factors, lifestyle factors and work type. In the second step, multivariate logistic regression was used to evaluate the association between exit from paid employment (dependent variable) and measures of ill-health (i.e., RD, other comorbidities and self-perceived health status) as independent variables, when adjusted to the other variables of interest (including age, sex, and region). In the final multivariable models, only variables statistically significantly associated with the dependent variable ($p < 0.05$) were considered. The models were built by means of a manual stepwise technique (backward elimination).

A better measure of the importance of a risk factor may be the population attributable fractions (PAF), which takes

into account both the strength of the association between risk factor and outcome and the prevalence of that risk factor in the population. PAF were calculated as the resulting proportional change in the probability of exit from paid employment after a counterfactual exercise where the presence of a risk factor is artificially eliminated from the sample. All statistical analyses were carried out using Stata 10 for Windows.

Results

At the time of the survey, 45.1 % of the Portuguese population with ages between 50 and 64 years old were not employed. Their baseline characteristics are presented in Table 1 where they are compared against those who were still with paid work. Among all regions of Portugal, the North region presented the highest prevalence of early exit from paid employment. Being older, lower education, manual type of work, lower household income, and female gender characteristics were more frequent within this group. However, this higher frequency in women (a group with more homemakers) may be partly explained by the unbalance on the different types of exit from employment between genders. There were no remarkable differences concerning marital status and lifestyle factors (i.e., obesity, alcohol, and smoking consumption) between groups (these variables were not included in the models shown in Table 2). On the other hand, concerning health substantial differences were observed, either measured through self-perceived health or through the presence of chronic diseases. Early retirees were remarkably worse in terms of their health conditions. More than a third (31.6 %) of nonemployed individuals reported "poor" to "very poor" health, whereas about half of that proportion (16.4 %) was found among those still employed (Table 1). Higher prevalence of all assessed comorbidities was found in the group of individuals with early exit from paid work. Additionally, higher average number of comorbidities per capita was found in this group (comorbidity score = 1.9 vs. 1.4, $p < 0.001$). Particularly, RD were more frequently self-reported among those not currently at paid work than in the remaining population (43.4 vs. 32.1 %). Among all those self-reporting RD, more than half (52.6 %) were not employed. Mental health disorders (i.e., anxiety and depression) were also more frequent on those out of work.

In Table 2, it is possible to verify the results obtained from the uni- and multivariate logistic regressions. In line with the descriptive results presented in Table 1, North region, higher age, female, lower education, manual type of work, lower household income, and worse health status were associated with early exit from paid employment. Age adjustment didn't cause many differences in the *odds ratios* of each variable (Table 2—Model 2). However, unsurprisingly, we found high correlation (multicolinearity) among covariates and only some predictors remained in the final multivariate models (Table 2—Model 3, 4 and 5).

A higher number of comorbidities is a significant predictor of early exit from paid employment after adjustment to other covariates (OR 1.08; CI 1.02–1.15, $p = 0.011$). Table 2—Model 4), but when specific comorbidities were included in the multivariate analysis (Table 2—Model 3), most of the chronic diseases were no longer statistically significant, with the exception of renal impairment (OR 1.74; CI 1.05–2.87, $p = 0.031$) and previous stroke (OR 2.09; CI 1.25–3.52, $p = 0.005$). In both models and regardless the proxy used for comorbidity, region, age, gender, education, and self-perceived health status showed the strongest association with early exit from work.

The high association between ill-health and early exit from paid employment, when measured by less than "good" self-perceived health, translates in ORs varying between 1.25 and 1.69 for "fair" and between 1.96 and 3.31 for "bad/very bad", depending on the type of analysis considered (i.e., uni- or multivariate regression models. See Table 2).

As expected, high correlation was observed between RD and other important factors, such as the presence of other illnesses (coexistence of RD with other chronic conditions is well-known in the literature) [53, 54]. Therefore, in the RD-specific model (Table 2—Model 5), after adjustment and considering cofactors with low variance inflation factor (i.e., VIF <5 in order to avoid multicolinearity), only region, age, education, and household income remained statistically significant. In this model, adjusted OR for RD was 1.31 (1.12–1.52, $p = 0.001$). The PAF of RD calculated with adjusted and unadjusted ORs were 5 and 9.8 %, respectively.

Of note, we tested for interactions between RD and gender; RD and age; and RD and type of work, but none of the interaction variables remained significant in the final multivariable models (*data not shown*).

We have also tested the association of RD with a more restrictive definition of early exit work, using only formal retirement as the outcome variable in the regressions. In spite of the fact that our sample had a considerable number of other forms of exit from labor market, in particular female homemakers (Table 3), we still observed a significant association between RD and this more restrictive definition of pure early retirement (Table 4). This suggests that RD remains associated with early departure from paid employment regardless the definition used.

Discussion

The current study, which was based on a large and representative sample of the Portuguese population approaching

Table 1 General description of the sample by employment status: Portuguese National Health Survey ($n = 8{,}003$) ages 50–64

	Exit from paid employment % (*N*)	Paid employment % (*N*)	*p* value
Employment status	45.1 (838,358)	54.9 (1,021,403)	NA
Area of residence			
North	38.5 (322,787)	29.5 (301,592)	$p < 0.001$
Center	13.0 (108,632)	20.5 (209,142)	
Lisbon region	36.5 (39,089)	36.8 (375,693)	
Alentejo	4.7 (29,791)	5.1 (51,678)	
Algarve	3.6 (17,330)	4.5 (45,808)	
Azores	2.1 (17,330)	1.7 (17,137)	
Madeira	1.8 (14,745)	2.0 (20,349)	
Age			
50–54	22.8 (191,519)	47.8 (487,716)	$p < 0.001$
55–59	34.2 (286,708)	33.5 (342,403)	
60–64	43.0 (360,130)	18.7 (191,284)	
Gender (female)	62.6 (524,892)	44.1 (450,204)	$p < 0.001$
Educational level			
Primary school or less	77.9 (651,726)	65.2 (664,201)	$p < 0.001$
Medium	13.7 (114,658)	18.1 (184,345)	
High	8.5 (70,817)	16.7 (170,372)	
Marital status			
Single	5.1 (42,917)	5.4 (54,987)	NS $p = 0.06$
Married	82.8 (694,411)	83.0 (847,548)	
Divorced	5.0 (42,005)	6.7 (68,874)	
Widowed	7.0 (59,023)	4.9 (49,992)	
Occupational class			
Nonmanual worker	36.2 (197,566)	44.8 (456,533)	$p < 0.001$
Manual worker	63.9 (348,977)	55.2 (563,088)	
Self-perceived health status			
Very good/good	20.6 (140,144)	35.3 (244,408)	$p < 0.001$
Fair	47.7 (322,316)	48.3 (477,134)	
Poor/very poor	31.6 (219,424)	16.4 (162,074)	
Body mass index			
<25 kg/m^2	32.8 (266,239)	33.3 (336,650)	NS $p = 0.486$
25–30 kg/m^2	42.7 (355,191)	43.6 (440,165)	
≥0 kg/m^2	25.2 (209,742)	23.1 (233,172)	
Alcohol (daily consumption)	43.6 (365,570)	46.1 (470,694)	NS $p = 0.237$
Smoking status			
Not a smoker/occasional smoker	72.3 (606,127)	62.4 (637,117)	$p < 0.001$
Ex-smoker	16.8 (141,214)	21.3 (217,103)	
Current smoker	10.9 (91,015)	16.4 (167,181)	
Chronic diseases			
Rheumatic diseases	43.4 (363,587)	32.1 (328,198)	$p < 0.001$
Diabetes	16.0 (133,783)	11.1 (113,191)	$p < 0.001$
Asthma	7.7 (64,693)	4.7 (47,864)	$p = 0.004$
Hypertension	43.5 (364,704)	34.2 (349,487)	$p < 0.001$
Chronic pain	32.2 (269,877)	22.7 (232,053)	$p < 0.001$
Cancer	4.3 (36,298)	3.0 (30,275)	NS $p = 0.09$
Renal impairment	3.9 (32,661)	1.4 (14,223)	$p < 0.001$
Respiratory diseases	5.7 (47,634)	3.1 (31,603)	$p = 0.002$

Table 1 continued

	Exit from paid employment % (*N*)	Paid employment % (*N*)	*p* value
Stroke	3.6 (30,392)	1.6 (16,029)	$p = 0.002$
Myocardial infarction	2.0 (16,824)	1.5 (15,112)	NS $p = 0.291$
Anxiety	10.6 (89,006)	7.1 (72,333)	$p = 0.003$
Depression	16.2 (135,830)	12.6 (128,898)	$p = 0.014$
Household income (per month)			
≤€500	30.1 (246,406)	19.9 (196,433)	$p < 0.001$
>€500 and ≤€900	29.3 (239,261)	28.5 (280,996)	
>€900 and ≤€2000	31.0 (253,381)	35.4 (348,990)	
>€2000	9.6 (78,660)	16.2 (159,492)	

Prevalences of exit from paid work and other subjects' characteristics were computed as weighted proportions, in order to keep into account the sampling design of the survey ($N = 1{,}859{,}761$)

the statutory age of retirement (65 years old), suggests a strong association between ill-health and early exit from paid employment. This holds true for chronic rheumatic disorders, which seem to play a key role in early pathways of retirement. Thus, significantly higher ORs for ill-health variables were captured in this research, showing its impact in the Portuguese labor force participation. Of particular note, less than good self-reported health status is highly associated with early exit from paid work. This relationship is quite independent from other variables, including depression and anxiety, in almost all multivariate adjustment presented in this paper. As in previous research from other countries, the presence of specific chronic conditions was also highly associated with overall exit from paid employment, in particular, rheumatic conditions, renal impairment, and a history of stroke. Not surprisingly, these comorbidities, which cause considerable functional disability, may represent important sources of inactivity in Portugal. The specific focus of RD in this research allowed an estimation of a PAF from 5 to 9.8 %. This means that upon an alternative ideal exposure scenario, with no RD in the Portuguese population, there could be a reduction of up to almost a tenth of the overall risk of early exit from paid work, thereby potentially generating significant productivity gains.

Furthermore, the presence of other comorbidities seems to also contribute to the same sort of risk. For each additional chronic disorder (including chronic pain), there is an estimated increase in risk of approximately 8 %, after adjustment to other cofactors.

Interestingly, mental-related comorbidities (i.e., depression and anxiety) seem to have less association with exit from work compared with physical-related ones, mostly when adjusted to other cofactors. Although these results contrast with previous research done in northern Europe, especially for depression [10, 11, 36], they appear to be in line with some other evidence coming from southern Europe [23]. Our findings could be due to several reasons. Namely, the lack of societal valorization of mental diseases in Portugal may discourage patients to use it as a primary reason for retirement. In addition, physical impairment is much more likely to qualify for disability pensions than most forms of mental illnesses. Another possible reason may be based on the underlying strong association between physically disabling conditions and depression/anxiety, so that the former's stronger effect may actually mask separate effects of the latter. Moreover, one can also speculate that our inability to distinguish between mild-to-severe depression may have driven the results. Portugal's high prevalence of mild-to-moderate depression may "dilute" the possible higher effect of severe depression in early withdrawal from paid work.

Lifestyle factors such as obesity, smoking status, and alcohol consumption have already been shown to have an effect on some countries' retirement outcomes [11–15]. However, in this study, we found no significant relationship of these factors to exit from paid employment. In the case of smoking and alcohol, we cannot rule out that differences in exposure definition (quantity and duration) may, at least partially, explain this difference relative to other research.

Our final multivariate models revealed that higher education, higher household income, and having a nonmanual type of work are less associated with early exit from the labor force. Previous work has shown contradictory results on this regard. On the one hand, higher education and income, which are characteristics related to better working conditions, assure accumulation of more assets during lifetime allowing employees to leave their paid work earlier. However, on the other hand, a poor working condition is known to be a significant determinant of premature departure from working life. This has been observed in employees with physically demanding work or with monotonous and repetitive work [7, 9]. Additionally, exposure to manual

Table 2 Logistic regression analysis of the influence of individual characteristics and ill-health on the likelihood of exit from paid employment

	Model 1[a] univariate OR (95 % CI)	Model 2[b] multivariate OR (95 % CI)	Model 3[c] multivariate OR (95 % CI)	Model 4[d] multivariate OR (95 % CI)	Model 5[e] multivariate OR (95 % CI)
Area of residence					
North	1	1	1	1	1
Center	0.49 (0.39–0.61)	0.43 (0.34–0.54)	0.51 (0.41–0.62)	0.51 (0.42–0.63)	0.53 (0.43–0.64)
Lisbon region	0.76 (0.61–0.95)	0.70 (0.56–0.88)	0.75 (0.62–0.92)	0.76 (0.62–0.93)	0.77 (0.63–0.94)
Alentejo	0.71 (0.56–0.89)	0.65 (0.51–0.83)	0.72 (0.59–0.89)	0.73 (0.60–0.90)	0.72 (0.59–0.88)
Algarve	0.61 (0.49–0.76)	0.55 (0.44–0.70)	0.65 (0.53–0.80)	0.67 (0.55–0.82)	0.62 (0.51–0.76)
Azores	0.94 (0.75–1.19) NS	0.95 (0.74–1.21) NS	1.08 (0.88–1.31) NS	1.09 (0.89–1.32) NS	1.04 (0.86–1.27) NS
Madeira	0.68 (0.53–0.86)	0.65 (0.50–0.85)	0.80 (0.63–1.09) NS	0.83 (0.66–1.05) NS	0.85 (0.68–1.07) NS
Age					
50–54	1	*	1	1	1
55–59	2.13 (1.73–2.62)	*	1.88 (1.57–2.25)	1.84 (1.53–2.20)	1.86 (1.55–2.22)
60–64	4.79 (3.87–5.94)	*	4.48 (3.70–5.41)	4.37 (3.61–5.29)	4.32 (3.58–5.22)
Gender (Female)	2.12 (1.80–2.51)	2.25 (1.89–2.68)	1.99 (1.70–2.32)	1.88 (1.60–2.19)	*
Educational level					
Primary school or less	1	1	1	1	1
Medium	0.64 (0.50–0.82)	0.70 (0.55–0.89)	1.04 (0.84–1.28) NS	1.04 (0.84–1.29) NS	0.97 (0.78–1.20) NS
High	0.42 (0.33–0.55)	0.46 (0.36–0.59)	0.70 (0.56–0.89)	0.70 (0.56–0.89)	0.68 (0.52–0.89)
Occupational class					
Nonmanual worker	1	1	§	§	*
Manual worker	1.43 (1.18–1.73)	1.38 (1.13–1.67)	§	§	*
Self-perceived health status					
Very good/good	1	1	1	1	*
Fair	1.69 (1.43–2.01)	1.52 (1.20–1.91)	1.33 (1.11–1.61)	1.26 (1.04–1.53)	*
Poor/very poor	3.31 (2.71–4.04)	2.87 (2.19–3.75)	2.07 (1.64–2.60)	1.91 (1.49–2.47)	*
Chronic diseases					
Rheumatic diseases	1.62 (1.36–1.92)	1.38 (1.15–1.64)	§	*	1.31 (1.12–1.52)
Diabetes	1.52 (1.19–1.95)	1.30 (1.01–1.68)	§	*	*
Asthma	1.70 (1.18–2.45)	1.66 (1.14–2.41)	§	*	§
Hypertension	1.48 (1.25–1.75)	1.26 (1.06–1.50)	§	*	*
Chronic pain	1.62 (1.34–1.94)	1.53 (1.26–1.85)	§	*	§
Cancer	1.48 (0.94–2.33) NS	1.38 (0.88–2.18) NS	§	*	§
Renal impairment	2.87 (1.56–5.27)	2.71 (1.49–4.93)	1.74 (1.05–2.87)	*	§
Respiratory diseases	1.89 (1.25–2.85)	1.59 (1.04–2.44)	§	*	§
Stroke	2.36 (1.34–4.16)	1.96 (1.06–3.62)	2.09 (1.25–3.52)	*	§
Myocardial infarction	1.36 (0.77–2.43) NS	1.02 (0.54–1.91) NS	§	*	§
Anxiety	1.56 (1.16–2.09)	1.46 (1.09–1.96)	§	*	*
Depression	1.34 (1.06–1.69)	1.41 (1.10–1.81)	§	*	*
Comorbidity score	1.94 (1.68–2.24)	1.72 (1.48–1.99)	*	1.08 (1.02–1.15)	*
Household income (per month)					
≤€500	1	1	§	§	1
>€500 and ≤€900	0.68 (0.54–0.85)	0.73 (0.58–0.93)	§	§	0.84 (0.69–1.04) NS
>€900 and ≤€2000	0.58 (0.46–0.72)	0.65 (0.52–0.83)	§	§	0.78 (0.64–0.96)
>€2000	0.39 (0.29–0.53)	0.45 (0.33–0.60)	§	§	0.66 (0.48–0.89)

OR odds ratio, *CI* confidence interval

* Cofactor not included in the model

§ Cofactor excluded in the stepwise method (backward elimination with $p > 0.05$)

[a] All variables separately (unadjusted model)

[b] Adjusted for age

[c] Adjusted for chronic diseases, demographic variables, self-perceived health, and socioeconomic indicators

[d] Adjusted for comorbidity score, demographic variables, self-perceived health, and socioeconomic indicators

[e] RD-specific model adjusted for all remaining cofactors with low variance inflation factor (i.e., VIF < 5)

Table 3 Description of the sample by type of employment status for ages 50–64: Portuguese National Health Survey ($n = 8{,}003$)

	Employed	Exit from paid employment				
		Officially retired	Unemployed	Permanently disabled	Homemaker	Other[a]
Male	64.6 % (571,198)	23.8 % (209,854)	9.1 % (80,047)	1.6 % (13,912)	0.05 % (428)	0.8 % (7,949)
Female	46.2 % (450,205)	15.7 % (152,783)	6.2 % (60,441)	1.5 % (14,905)	28.8 % (279,688)	1.6 % (13,843)
Total	54.9 % (1,021,403)	19.5 % (362,636)	7.6 % (140,487)	1.6 % (28,816)	15.1 % (280,115)	1.3 % (21,792)

Prevalences of different forms of exit from paid work were computed as weighted proportions, in order to keep into account the sampling design of the survey ($N = 1{,}859{,}761$)

[a] For instance, people working for a relative without receiving any payment

and poor working conditions was also shown to increase intentions to leave earlier employment trajectories [7–9, 55–57]. Therefore, previous data showed that these financial and working conditions variables can have opposite effects on the risk of early retirement. Nevertheless, our results demonstrate now that, at least in Portugal, these factors are more associated with early exit from work than the opposite.

Remarkably, marital status didn't seem to have much of an effect on the likelihood of early withdrawal from paid employment. Some studies have shown an effect of marital status on the risk of early retirement, but the employment status of the partner seems to play a more important role in this regard. In addition, the family context may also play an important role. Couples may coordinate their decisions and the partner may influence the choice of leaving the labor market [44, 58, 59]. However, this sort of information was not captured in the INS database.

We do not expect our results to be influenced by justification bias, a common limitation in this type of research. Some people may want to justify their early retirement through health problems and/or general self-reported lower health status. Since this research didn't use its own questionnaire and all the analysis was done based on the INS, which is not focused on retirement, we don't expect this limitation to have a significant impact on the overall results. Surveyed population couldn't realize any specific intention to relate their health with their corresponding working situation and shouldn't feel any pressure or need to justify their retirement condition. We also don't anticipate that self-reporting may be a significant limitation in this work, because most important tested risk factors, such as RD and other chronic disorders, are expected to inflict significant disability and/or impact on quality of life. Self-reporting is then considered to be a reliable marker of the actual presence of these comorbidities. We also don't assume answers to be subject to recall bias, since no information from the past, requiring any particular memory challenge, was used.

However, some limitations must be taken into account in interpreting the results of this study. First of all, this study may be limited by its cross-sectional design, which does not allow evaluation of the temporal relationship between onset of risk factors and time of exit from paid employment, which would be essential for establishing a cause–effect relationship. Nevertheless, onset of most forms of RD and main chronic disorders is likely to start before premature exit from paid employment. This limitation is expected to be more relevant for self-perception of health, late-onset diseases (i.e., cancer, stroke and MI), and mental disorders (i.e., depression and anxiety). Some researchers have also suggested retirement as a risk factor for poor health outcomes [25, 60, 61]. Thus, although our results are generally consistent with prospective data collected elsewhere, we cannot entirely rule out reverse causation bias for some cases. Lack of available national longitudinal data made this limitation impossible to turnaround. Secondly, the INS sampling methodology excluded people based on hospitals and retirement homes, so this study doesn't take into account this minority. Still, due to obvious reasons, this possible sampling bias is expected to weaken the association found between ill-health and exit from work. Thirdly, early exit from paid work is reportedly influenced by many other factors not included in these regression models, therefore maybe not all possible confounding was addressed in this research. However, adjustment was done with all available cofactors in the INS dataset, which according to the literature could influence retiring decisions, covering main areas of interest, including personal, health, financial, and working-related conditions. In fact, to our knowledge, this might be among one of the studies with higher number of addressed cofactors.

To our knowledge, this is the first study that was focused on the association of health and early exit from paid work in Portugal and one of the few in southern Europe. As described before, Portugal is at the forefront of this worldwide sustainability issue for social protection mechanisms concerning the increased incidence of early work exit not being compensated with the flow of new workers into employment. Therefore, all analyses performed in Portugal and subsequent potential interventions to discourage early out of paid employment can

Table 4 Logistic regression analysis by type of early exit from paid employment

	Early retirement		Early retirement + unemployment		Exit from paid employment[a]	
	Univariate logistic regression OR (95 % CI)	Multivariate logistic regression OR (95 % CI)	Univariate logistic regression OR (95 % CI)	Multivariate logistic regression OR (95 % CI)	Univariate logistic regression OR (95 % CI)	Multivariate logistic regression OR (95 % CI)
Rheumatic diseases	1.36 (1.15–1.62)	1.24 (1.01–1.52)	1.22 (1.04–1.42)	1.20 (1.01–1.43)	1.62 (1.36–1.92)	1.31 (1.11–1.52)
Age						
50–54	1	1	1	1	1	1
55–59	3.19 (2.44–4.18)	3.27 (2.46–4.33)	2.06 (1.67–2.54)	2.11 (1.70–2.61)	2.13 (1.73–2.62)	1.86 (1.55–2.22)
60–64	8.79 (6.79–11.37)	9.97 (7.56–13.2)	4.20 (3.43–5.15)	4.44 (3.59–5.51)	4.79 (3.87–5.94)	4.32 (3.58–5.22)
Gender (female)	0.61 (0.52–0.73)	0.54 (0.44–0.66)	0.61 (0.52–0.71)	0.56 (0.48–0.67)	2.12 (1.80–2.51)	*
Area of residence						
North	1	1	1	1	1	1
Center	0.74 (0.59–0.94)	0.68 (0.53–0.88)	0.59 (0.48–0.73)	0.55 (0.44–0.68)	0.49 (0.39–0.61)	0.53 (0.43–0.64)
Lisbon	1.00 (0.81–1.25) NS	0.85 (0.67–1.09) NS	0.86 (0.71–1.05) NS	0.77 (0.62–0.95)	0.76 (0.61–0.95)	0.77 (0.63–0.94)
Alentejo	1.07 (0.86–1.34) NS	1.08 (0.85–1.38) NS	0.94 (0.77–1.16) NS	0.92 (0.74–1.14) NS	0.71 (0.56–0.89)	0.72 (0.58–0.88)
Algarve	0.73 (0.58–0.92)	0.67 (0.52–0.86)	0.62 (0.51–0.76)	0.57 (0.46–0.70)	0.61 (0.49–0.76)	0.62 (0.51–0.76)
Azores	0.85 (0.68–1.06) NS	0.83 (0.65–1.07) NS	0.56 (0.46–0.69)	0.54 (0.44–0.68)	0.94 (0.75–1.19) NS	1.04 (0.86–1.27) NS
Madeira	0.59 (0.44–0.78)	0.60 (0.44–0.82)	0.42 (0.33–0.55)	0.42 (0.32–0.56)	0.68 (0.53–0.86)	0.85 (0.68–1.07) NS
Educational level						
Primary school or less	1	1	1	1	1	1
Medium	1.32 (1.05–1.65)	1.59 (1.22–2.08)	1.26 (1.02–1.55)	1.48 (1.18–1.85)	0.64 (0.50–0.82)	0.97 (0.78–1.20) NS
High	1.13 (0.89–1.44) NS	1.26 (0.91–1.75) NS	0.90 (0.72–1.14) NS	1.14 (0.89–1.45) NS	0.42 (0.33–0.55)	0.68 (0.52–0.89)
Household income						
≤€500	1	§	1	§	1	1
>€500 and ≤€900	0.99 (0.79–1.26) NS	§	1.03 (0.83–1.27) NS	§	0.68 (0.54–0.85)	0.84 (0.69–1.04) NS
>€900 and ≤€2000	1.18 (0.94–1.48) NS	§	1.06 (0.86–1.30) NS	§	0.58 (0.46–0.72)	0.78 (0.64–0.96)
>€2000	1.35 (1.01–1.78)	§	0.87 (0.66–1.13) NS	§	0.39 (0.29–0.53)	0.66 (0.48–0.89)
Other comorbidities						
Asthma	1.57 (1.13–2.18)	1.61 (1.10–2.35)	1.37 (1.00–1.87)	§	1.70 (1.18–2.45)	§
Chronic pain	1.36 (1.14–1.63)	1.38 (1.12–1.70)	1.32 (1.11–1.56)	§	1.62 (1.34–1.94)	§
Cancer	1.94 (1.29–2.89)	2.00 (1.26–3.16)	1.69 (1.15–2.48)	§	1.48 (0.94–2.33) NS	§
Renal impairment	3.36 (2.15–5.25)	2.96 (1.74–5.05)	2.95 (1.89–4.59)	2.60 (1.62–4.16)	2.87 (1.56–5.27)	§
Stroke	3.56 (2.24–5.66)	2.94 (1.72–5.03)	3.47 (2.18–5.51)	3.02 (1.85–4.95)	2.36 (1.34–4.16)	§

OR Odds Ratio; *CI* confidence interval

* Cofactor not included in the model (VIF > 5)

§ Cofactor excluded in the stepwise method (backward elimination with $p > 0.05$)

[a] Exit from paid employment includes: early retirees, unemployed, permanently disabled, homemakers, and others

be a useful reference for policies to be undertaken elsewhere, especially in countries more similar from a socioeconomic and epidemiologic perspective, such as other southern European countries. Our results concerning the impact of ill-health on premature exit from paid work seem to be in line with at least some of the evidence previously published in Italy and Spain [23, 49]. However, as already mentioned, there is still scarce data on this subject in the context of southern European countries. These nations are currently facing an aging population, high rates of unemployment, and huge economic pressures, which contribute to a common need to generate and share evidence to support policies for increasing productivity and postponing retirement, including interventions on those individuals with disability. In addition to this, there are peculiarities in the national social systems that are generally common among Portugal and other southern European countries. For example, these countries behave similarly in the two main disability policy indicators originally constructed by OECD [62]: the first indicator covers compensation measures or benefit programs, which summarizes subjective indicators of disability and sickness benefit values and availability, where Portugal and Spain score above the OECD average (higher score means greater system generosity) and the second covers the employment and integration schemes, including the availability of special employment programs, vocational rehabilitation, and in work benefits, where Portugal shares with Italy lowest scores in Europe [26]. These similarities also justify a shared model based on collective knowledge about the conditions and determinants of early exit work in southern Europe.

By using a national population-based survey (high external validity), this research may aid building that model and may support appropriate policies, while at the same time can also help to customize policies for subsets of the population (i.e., different risk groups). For instance, all activities aiming to decrease the risk of early exit from paid work should take into account the gender and the type of work of each particular subpopulation under analysis. On this regard, more attention should be brought to female manual workers, in particular in the northern region, a subgroup expected to be more vulnerable to RD (for the age group considered, there is a RD prevalence of 55 % in female manual workers from north of Portugal). In Spain, other published work attained similar results regarding this vulnerable subgroup [49].

By specifically addressing RD, which affects almost half of the Portuguese population with age close to retirement, it was possible to isolate the association of such disorders as a whole group of diseases to the likelihood of early withdrawal from work. Nonetheless, future research should discriminate those forms of RD, which are more disabling and consequently more likely to be associated with anticipated exit from work. This will allow society and labor market policies to be geared toward helping employees with highly disabling RD to remain in work or reintegrate into the workforce. This sort of policies will be essential for all those unemployed who are unsuitable to work due to disability. According to latest official statistics, unemployment rates in the age group of 55–64 years old have doubled since 2005 [63]. Measures aiming to shift from compensation-oriented policies toward integration-oriented policies will have a positive effect on this trend. Some intervention programs specifically addressing rheumatic patients have been already tested with proven success. In Spain, rheumatologists following detailed proceedings in a specialist-run early intervention program had a clear effect on temporary work disability [64]. Certainly, this sort of interventions targeting specifically these conditions will provide long-term productivity gains to society. These productivity gains may in fact counterbalance the costs of such interventions.

Conclusion

This research foresees great potential concerning the risk reduction of early exit from paid work by eliminating or controlling chronic diseases in the population, in particular those causing high disability such as RD. Thus, health and social protection policies should identify high-risk populations when it comes to define policies to dissuade early retirement.

Acknowledgments The authors thank Helena Canhão, Ana Paula Martins, Jaime Branco and Pedro Aguiar for their criticism and suggestions.

Conflict of interest The authors declare that they have no conflict of interest.

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PART 2 - THE INDIRECT COSTS OF EARLY RETIREMENT ATTRIBUTABLE TO RHEUMATIC DISEASES

Article B: Indirect Costs Associated with Early Exit from Work Attributable to Rheumatic Diseases

Pedro A. Laires, Helena Canhão, Miguel Gouveia

European Journal of Public Health. Vol 25(4):677-82, 2015

The European Journal of Public Health Advance Access published January 28, 2015
European Journal of Public Health, 1–6

doi:10.1093/eurpub/cku241

Indirect costs associated with early exit from work attributable to rheumatic diseases

Pedro A. Laires[1], Helena Canhão[2,3], Miguel Gouveia[4]

1 Faculdade de Medicina da Universidade de Lisboa, Lisbon Academic Medical Center, Lisbon, Portugal
2 Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal
3 Rheumatology Department, Hospital de Santa Maria, Lisbon, Portugal
4 Catolica Lisbon School of Business and Economics, Lisbon, Portugal

Correspondence: Pedro A. Laires, Faculdade de Medicina da Universidade de Lisboa, Lisbon Academic Medical Center, Av. Professor Egas Moniz, 1649-028 Lisbon, Portugal, Tel: (+351) 919783234, Fax: (+351) 217985114, e-mail: laires.pedro@gmail.com

Background: Rheumatic diseases (RD) cause physical disability that may lead to early exit from work, generating indirect costs to society. We aimed to measure these costs in a population approaching the statutory retirement age. **Methods:** The analysis was based on the prevalence of self-reported RD using a bottom-up approach. Health and sociodemographic data were retrieved from the fourth National Health Survey (INS), for all people between 50 and 64 years of age (3762 men and 4241 women), whereas an official national database was used to estimate productivity values by gender, age group and region, using the human capital approach. The effects of RD on the likelihood of early exit from paid employment and the attributable fractions estimates were obtained at the individual level by logistic regression. **Results:** At the time of the survey, 37.2% of the population aged 50–64 years self-reported at least one RD. Among these, 52.6% were not employed, compared with 40.7% of those without RD ($P < 0.001$). The annual indirect costs following premature exit from work attributable to RD were €650 million (€892 per RD patient). Early retirement amounted to €367 million, whereas early retirement and unemployment totalized €385 million (€504 and €528 per RD patient, respectively). Females are responsible for about 60% of these costs; however, males contribute with higher individual productivity losses. **Conclusion**: Early exit from work attributable to RD amounts to approximately 0.4% of the national GDP. The public health concern and the economic impact highlight the need to prioritize investments in health and social protection policies targeting patients with rheumatic conditions.

Introduction

Rheumatic diseases (RD) are characterized by pain and physical disability that may lead not only to a substantial consumption of health resources but also to productivity losses and early retirement.[1–3] Knowledge about the economic burden of this group of disorders has progressed in recent years confirming that the total economic burden of RD is often more substantial than other chronic conditions, including cardiovascular diseases and cancer; and that the impact of the disability caused by these conditions is significant on both direct and indirect costs, such as early exit from work.[4] Foregone productivity due to premature withdrawal from work decreases the wealth of society and thus should be considered in the estimation of the economic impact of these illnesses.[5]

Available evidence suggest that RD play a key role on overall early exit from work because usually they are both highly prevalent and disabling, in particular for occupations where working conditions are difficult to modify or adjust to the impaired work abilities of employees.[6,7] Nevertheless, most published works on indirect costs address specific rheumatic conditions (e.g. rheumatoid arthritis[8–10] and ankylosing spondylitis[11]) and there is a general lack of research about the costs associated with RD as a whole. Considering all RD, instead of dealing with specific RD forms, puts the focus on common characteristics of all forms of rheumatic conditions (for instance, highly prevalent in lower social classes, progressive physical disability).

Considerable changes in labour force rates have been observed in the last decades with a shrinking number of economically active people supporting a growing economically dependent elderly population.[12] This has led to heavy financial demands and to Social Protection systems sustainability problems for countries with high unemployment, early retirement and disability pensions, likely influenced by progressively prevalent chronic diseases, such as RD. Nowadays, in developed countries, over a third of the population approaching the statutory retirement age suffers some type of RD.[13–16] This situation will deteriorate in the coming future and therefore RD are expected to have a growing impact in indirect costs, in particular those caused by premature departure from the labour market. This makes RD good candidates to be the target of specific public health policies, which in turn should be preceded by research supporting informed decision making. Calculating this specific type of indirect costs attributable to RD may help to prioritize not only this group of illnesses as a whole but also aid to identify particular subgroups at higher risk, thereby justifying higher investments on activities to reduce their risk of early withdrawal from work.

The main aim of this study is to measure the indirect costs associated with early exit from work attributable to all RD in a population approaching the statutory retirement age.

Methods

Sample

The source of data for this study was the Fourth Portuguese National Health Survey (INS), which was conducted in 2005 and 2006 in all regions of Portugal. The methodology of the INS has been detailed elsewhere.[17,18] Briefly, the primary sampling unit was the housing unit, which were randomly selected within each geographically defined unit. Subjects living in the sampling unit were then surveyed by trained staff. The sample was considered representative of the main regions of Portugal.[18,19]

In this study, the subsample of all INS surveyed people approaching the statutory pension age, between 50 and 64 years, was analysed. The sample under analysis composed of 3762 men and 4241 women. Cases of RD were defined according the participant's self-reported history of any RD ('Do you or did you have any rheumatic disease (e.g. osteoarthritis, tendinitis)?'

Indirect costs

Early retirement was considered as being out of paid work before age 65 years, which is the most common statutory retirement age, including Portugal. There are different channels of exiting from the labour market, including unemployment, disability and pure early retirement.[19–21] These pathways are related to the same economic behaviour, which implies an exit from the labour market in the later stages of working life and subsequent loss of productivity for society. However, it was still considered relevant and more informative to separately analyse and report results for three main types of early exit from work: Type 1, pure retirement; Type 2, pure retirement and unemployment and Type 3, all forms of exit from paid employment.

We adopted the society's perspective and used the human capital approach to estimate productivity costs by valuing healthy time lost due to the disease using market wage rates, which can be viewed as the loss of an investment in a person's human capital.[22] The friction cost approach has been proposed as an alternative to calculate indirect costs; however, it is considered less appropriate to estimate the productivity losses for retirees and other forms of early exit from paid employment, which was the focus of our research.[23–25]

The value of lost production was assessed by obtaining the market wage rates from national public sources concerning year 2005.[26] These figures needed to be adjusted for social security contributions, since the economic cost of lost production is calculated on gross incomes and includes employers' contributions to social security. We obtained an annual average value of €19 455 for men and a €12 899 for women, for ages between 50 and 64 years. All unit values of lost production were stratified by age range, gender and geographic region (Supplementary Appendix S1).

Estimation of the sole impact of RD on the probability of early exit from paid employment was assessed using logistic regression models for the three types of outcome explained earlier (Supplementary Appendix S2). The following relevant covariates were included in the initial models: age, gender, region, other comorbidities, self-perceived health status, lifestyle factors, marital status, socioeconomic characteristics and occupational social class. In the final logistic models, only covariates with a statistically significant association to the dependent variable ($P < 0.05$) were considered.

A good measure of the impact of RD in the early exit from paid employment may be the population attributable fractions (PAF), which take into account both the strength of the association between RD and early exit from work, as measured in the logistic models, and the prevalence of RD in the surveyed population. PAF were calculated as the resulting proportional change in the probability of exit from paid employment after a counterfactual exercise where the presence of RD is artificially eliminated from the sample. This recalculated probability of early work exit was used to estimate the indirect costs attributable to RD. Thus, annual indirect costs associated with early exit from work and attributable to RD were obtained after multiplying each observation's probability change with the corresponding unit value of production (previously assigned in the INS sample according to age group, gender and geographic region).

Descriptive analysis was also performed comparing the RD population against the non-RD population. All variables were tested at the bivariate level using the chi-square test. Prevalence of exit from work and other characteristics were computed as weighted proportions, to take into account the sampling design of the survey.

Table 1 General description of the sample by presence or absence of RD for ages 50–64 years: National Health Survey ($n = 8003$)

	RD % (*N*)	Non-RD % (*N*)	*P* value
Prevalence	37.2 (691 786)	62.8 (1 167 975)	
Age			
50–54	27.6 (191 188)	41.8 (488.047)	$P < 0.001$
55–59	35.4 (244 632)	32.9 (384.479)	
60–64	37.0 (255 965)	25.3 (295.448)	
Gender (female)	70.1 (485 180)	42.0 (489 917)	$P < 0.001$
Educational level			
Primary school or less	78.6 (543 636)	66.3 (772 291)	$P < 0.001$
Medium	12.9 (89 389)	18.0 (209 614)	
High	8.5 (58 760)	15.7 (182 429)	
Marital status			
Single	4.4 (30 659)	5.8 (67 245)	$P < 0.001$
Married	83.1 (574 573)	82.8 (967 387)	
Divorced	5.5 (37 931)	6.3 (72 949)	
Widower	7.0 (48 622)	5.2 (60 393)	
Occupational class			
Non-manual worker	34.8 (190 079)	45.5 (464 020)	$P < 0.001$
Manual worker	65.2 (356 435)	54.5 (555 630)	
Self-perceived health status			
Very good/good	12.7 (92 463)	38.6 (436 611)	$P < 0.001$
Fair	50.3 (366 495)	46.6 (526 506)	
Poor/very poor	37.0 (269 752)	14.9 (167 931)	
Other chronic diseases			
Diabetes	15.9 (109 865)	11.7 (137 108)	$P < 0.001$
Asthma	9.4 (65 174)	4.1 (47 383)	$P < 0.001$
Hypertension	47.1 (325 960)	33.2 (388 231)	$P < 0.001$
Chronic pain	39.2 (270 838)	19.8 (231 092)	$P < 0.001$
Cancer	4.5 (31 286)	3.0 (35 287)	$P = 0.001$
Renal impairment	4.1 (28 073)	1.6 (18 811)	$P < 0.001$
Respiratory diseases	7.1 (48 796)	2.6 (30 440)	$P < 0.001$
Stroke	2.0 (13 938)	2.8 (32 482)	$P = 0.094$
Myocardial infarction	1.3 (9298)	1.9 (22 637)	$P = 0.906$
Anxiety	15.7 (108 721)	4.5 (52 618)	$P < 0.001$
Depression	21.8 (150 709)	9.8 (114 018)	$P < 0.001$
Household income (per month)			
≤ €500	25.9 (175 884)	23.7 (59 070)	$P < 0.001$
> €500 and ≤ €900	31.0 (209 957)	27.6 (310 299)	
> €900 and ≤ €2000	34.4 (233 566)	32.8 (368 805)	
> €2000	8.7 (59 070)	15.9 (179 083)	

All results are based on weighted data. Prevalence of RD and subjects' characteristics were computed as weighted proportions, to keep into account the sampling design of the survey ($N = 1\,859\,761$).

Results

At the time of the survey, 37.2% of the population with ages between 50 and 64 years self-reported at least one RD. The baseline characteristics of RD and non-RD sub-populations are presented in more detail in table 1. As expected, RD were more prevalent among older people and women. The same applies for those with lower education, lower household income and manual type of work. RD are highly associated with other comorbidities, such has chronic pain, hypertension, depression and anxiety. Almost all disorders surveyed were more often self-reported among those with RD (table 1), and higher average number of comorbidities per capita was found in the RD group (comorbidity score = 2.7 vs. 0.9, $P < 0.001$). Additionally, more than a third (37%) of RD individuals reported 'poor' to 'very poor' health, whereas less than half of that proportion (14.9%) was found among those without RD, meaning a clear worse self-perceived health associated with RD.

Table 2 Description of the sample by type of exit from work for ages 50–64 years: National Health Survey ($n = 8003$)

		Type 1, % (*N*)	Type 2, % (*N*)	Type 3, % (*N*)
RD	Males	33.9 (69 983)	42.0 (86 707)	44.9 (92 770)
	Females	17.9 (87 041)	24.3 (117 932)	55.8 (117 932)
	All gender	22.7 (157 024)	29.6 (204 639)	52.6 (363 587)
Non-RD	Males	20.6 (139 871)	30.0 (203 193)	32.6 (220 695)
	Females	13.4 (65 742)	19.5 (95 291)	51.9 (254 075)
	All gender	17.6 (205 613)	25.6 (298 485)	40.7 (474 770)
Global (RD + non-RD)	Males	23.7 (209.854)	32.8 (289.900)	35.4 (313.465)
	Females	15.7 (152.783)	21.9 (213.223)	53.8 (524.892)
	All gender	19.5 (362 636)	27.1 (503 124)	45.1 (838 358)

All results are based on weighted data. Type 1, pure retirement; Type 2, pure retirement + unemployment; Type 3, all forms of exit from paid employment.

Table 3 Summary of OR, population attributable fractions and indirect costs associated with RD (by definition of exit from work)

	Type 1 (early retirement)	Type 2 (early retirement + unemployment)	Type 3 (exit from paid employment)[a]
RD	22.7%	29.6%	52.6%
OR adjusted (unadjusted)	1.24 (1.36)	1.20 (1.22)	1.31 (1.65)
PAF adjusted (unadjusted)	5.9% (9.7%)	4.6% (5.5%)	5.0% (9.8%)
Overall indirect costs	367M€	385M€	650M€
Indirect costs per RD patient	504€	528€	892€

M€, millions of euros.
a: Exit from paid employment includes early retirees, unemployed, permanently disabled, homemakers and others.

Exit from work

Almost half of the surveyed population with ages between 50 and 64 years were out of paid work (45.1%, table 2). Among those who self-reported RD, 52.6% were not employed, compared with 40.7% of those without RD ($P < 0.001$, table 2—Type 3). In particular, 22.7% of RD participants declared to be officially retired (i.e. Type 1) compared with only 17.9% of those without RD. When considering all forms of exit from paid employment, women are more present than men, most likely due to higher proportion of female housewives; however, men are more likely to be out of work when narrow definitions of exit of work are used (Type 1: 23.7% vs. 15.7%; Type 2: 32.8% vs. 21.9%; Type 3: 35.4% vs. 53.8%, respectively, for men and women). This observation stills holds true if the population with RD is analysed separately from the non-RD subpopulation (table 2).

Logistic models and attributable fractions

In this nation-wide representative sample, a high association was obtained between RD and early exit from work, regardless of the definition used. For example, when using the Type 3 definition, the univariate odds ratio (OR) for RD was 1.62 (CI: 1.36–1.92, $P < 0.001$, Supplementary Appendix S2). This OR became 1.31 (CI: 1.12–1.52, $P < 0.001$) when adjusted. Also regarding Type 3, the PAF of RD calculated with adjusted and unadjusted ORs were 5% and 9.8%, respectively (table 3). The observed average probability of the sample to be out of paid work (Type 3) according to the model developed was 46.9%, whereas after transforming all observations into non-RD status, the model delivered a reduced average probability of 44.6%. After summing the products of each observation's probability change with the corresponding unit value of production (Supplementary Appendix S1), an overall estimate of €650 million per year of indirect costs caused by premature exit from work attributable to RD was obtained. This represents an annual indirect cost per person with RD of €892. When using other definitions of early exit from work, estimates of annual indirect costs of €367 million for pure reforms (Type 1) and €385 million for pure reforms and unemployment (Type 2, figure 1) were found; with annual indirect costs per person with RD of €504 and €528, respectively (table 3). Figure 1 depicts the evolution of estimated indirect costs attributable to RD by early out of work type. Females have higher indirect costs than males, particularly when using the Type 3 definition (€403 million vs. €247 million, respectively).

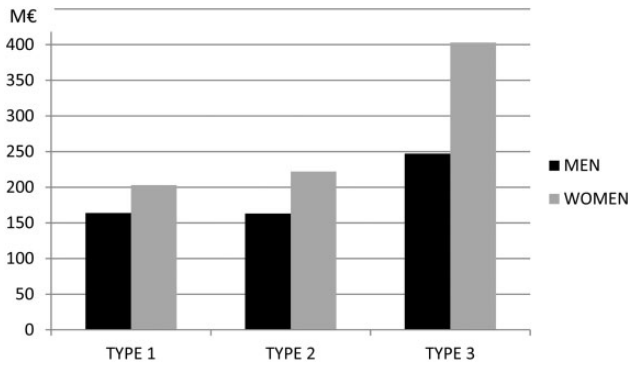

Figure 1 Indirect costs due to early exit from work attributable to RD (by gender). M€, millions of euros; Type 1, pure retirement; Type 2, pure retirement + unemployment; Type 3: all forms of exit from paid employment

Figure 2 shows the gender and age group contributions for the overall productivity losses according to each type of exit from work definition. Not surprisingly, both advanced age and female gender are associated with higher indirect costs. However, costs per person with RD are higher for men (€788 vs. €390 for Type 1; €784 vs. €426 for Type 2 and €1185 vs. €775 for Type 3), regardless of the age group considered (Supplementary Appendix S3).

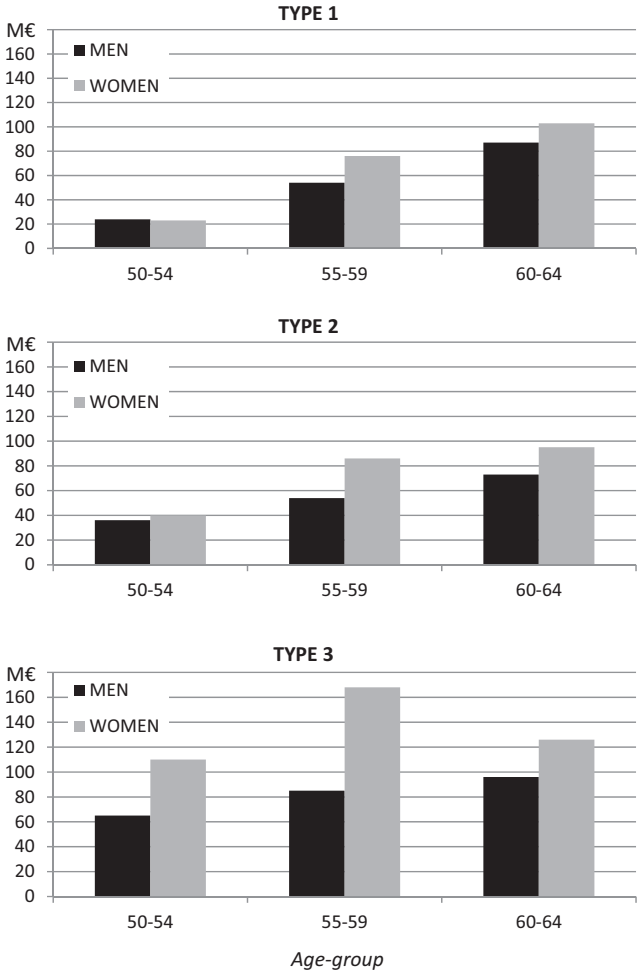

Figure 2 Indirect costs attributable to RD for different age groups (by type of early exit from work and gender). M€, millions of euros; Type 1, pure retirement; Type 2, pure retirement + unemployment; Type 3, all forms of exit from paid employment

Discussion

This study estimated that RD-related productivity losses due to early exit from paid employment are potentially associated with an annual cost between €367 million and €650 million (depending on the type of early exit from work considered). More than half of the sample with RD was not employed at the time of the survey and that translates into substantial costs for society. This research is based on a large and representative sample of the country's population approaching the statutory age of retirement, and thus, it is likely to reflect accurately the economic impact on Portuguese society. Considering the timeframe of the survey (2005/2006), this sort of costs is about 0.4% of the national GDP.

As RD are more prevalent in women, overall indirect costs split by gender were unbalanced with greater overall economic burden on females. The trend to even wages between genders and the worsening of the epidemiology of RD particularly in women lead to the expectation that these costs will grow faster in the coming future if nothing is done to the contrary, namely by controlling RD burden. The evidence around the gender decomposition of indirect costs per capita may be useful to raise awareness concerning the case of male RD patients, whose higher mean individual contribution of RD to indirect costs deserves concern. However, more importantly, along with the abovementioned reduction of gender inequalities in wages, female gender is more vulnerable to RD, meaning that public health policies on this regard should aim predominantly at women.

Of note, when housewives are not included in the analysis, men are more likely to be out of paid employment earlier than women. Ill health seems to play a particular role in early decisions of retirement among males. Men reporting more comorbidities and/or lower self-perceived health status are significantly more likely to be out of work earlier in their careers (data not shown). This topic in itself deserves further research as there may be great potential for targeted policies to achieve productivity gains.

Although age groups closer to retirement age have lower unit values of production, they are contributing more for overall indirect costs, because there is substantial higher prevalence or early retirees in these ages. Meaning that not only it is relevant to act in earlier ages but also it is still worthwhile to do so for older ones.

The reduced average probability of exit from work following the artificial removal of RD from the sample (counterfactual simulation) suggests that upon an alternative ideal exposure scenario, with no rheumatic disorders in the population, there could be a reduction of up to almost a tenth of the overall likelihood of early exit from paid work. We must highlight the fact that RD are not only highly associated with other comorbidities but that they are also established risk factors for some of these comorbidities. For example, RD are associated with an increased risk of chronic pain, cardiovascular risk, depression and anxiety.[27–32] In its turn, these comorbidities are also associated with early exit from work.[33] This means that RD may contribute further to the increased risk of early work exit through these alternative ill-health routes and that the herein presented indirect costs could have risen if these other secondary effects of RD had been considered. For instance, the univariate OR for chronic pain is between 1.36 and 1.62, for Type 1 and Type 3 outcomes, respectively. This means that RD underlying chronic pain are also expected to be affecting labour force participation through this disability route.

Studies have shown that the total economic burden of RD is often more substantial than other chronic conditions due to both direct and indirect costs.[4] In fact, depending on the specific condition, the indirect costs of RD may equal or even exceed the direct costs.[34] However, most cost-of-illness studies on RD are restricted to specific rheumatic forms and the literature still suffers from a general lack of research on the indirect costs associated with RD as a whole. To our knowledge, the current research is among the few studies of the indirect costs of RD specifically analysing early exit from work. Nonetheless, some authors have addressed the impact of RD in similar forms of indirect costs and they all came up with high estimates. For example, in 1998, a major share of the total cost of musculoskeletal disorders in Canada came from indirect costs (roughly 2.4% of the Canadian gross domestic product at that time).[35] This large share of indirect costs is in line with results from seminal studies in the United States done by Rice[36,37] and Yelin *et al.*[38,39] and it was even more pronounced in Sweden, where indirect costs (specially from early retirement) were accounted as 90% of all costs caused by RD.[40] More recently, in Australia, arthritis caused an annual loss of approximately 0.7% of GDP due to early retirement, which is in line with our results and much higher than the same type of costs caused by other disabling diseases,[41] such as cardiovascular disease (~0.06% of GDP),[42] diabetes (~0.08%)[43] and mental conditions (~0.1%).[44] Anyway, one as to bear in mind that comparing results of cost-of-illness studies is hampered by discrepancies between study designs, definition of RD, methodological choices and sources of data used.[5]

Our results were mostly based on self-reported data. We do not expect to have a significant bias due to low reliability of the participants' reported data, because RD are expected to inflict significant disability and/or impact in quality of life and therefore should be associated with high predictive values. On the other hand, we do not expect our results to be influenced by justification bias (i.e. some people may want to justify their early retirement through health problems, which is a common limitation in this type of research),

as this study was based on the INS, which was not focused on retirement and did not generate any pressure for responders to justify their retirement condition. However, some limitations must be taken into account in interpreting the results of this study. First, this study may be limited by its cross-sectional design, which does not allow evaluation of the temporal relationship between the onset of RD and the timing of labour force departure, meaning that some cases may have had RD onset after exit from work. Lack of available national longitudinal data made this limitation impossible to overcome. Nevertheless, onset of most forms of RD is likely to start before the statutory age of retirement. Second, early exit from paid work is reportedly influenced by many other factors not included in the regression models used, therefore maybe not all possible confounders were addressed in this research. However, adjustment was done with a considerable number of available cofactors in the INS dataset. In fact, to our knowledge, this might be among one of the studies with higher number of addressed cofactors. Third, the human capital method has been criticized for its overestimation of indirect costs,[24] since the real paid production loss to society is likely to be lower (for instance, for long-term absence, the work can be done by someone drawn from the unemployment pool or by reallocating existing employees). Nevertheless, as explained before, to address the objectives of this study, we considered this approach as the most appropriate and widely used method.[45] Gender wage differences impact the estimates in particular when studying RD, a disease more likely affecting women with lower average wages. Because there is no definitive method to solve this methodological dispute, we opted for a more conservative approach by allowing gender differences on unit production values. Finally, unit values of production were estimated through official statistics based on gender, region and age group. Necessarily, this methodology is a rough estimate of individual unit values of production. Still, from all available options, to our knowledge, this approach is the most appropriate.

This comprehensive population-based research underlines the high economic burden of RD concerning early retirement, justifying more attention when discussing policies facing the most relevant sustainability challenges of ageing western countries. Demographic trends and the epidemiological shift to an enduring chronic diseases paradigm will worsen this scenario if nothing is done.

Rheumatic disorders are still undervalued in health policies. However, we cannot afford to be inactive regarding this topic any longer and should address possible interventions intended to stop early exit from work due to RD. A prolongation of working life in these patients must be accomplished without threatening their well-being. Some intervention programs specifically addressing rheumatic patients have already been put in place and tested.[46] For example, vocational rehabilitation delivered to RD patients at risk for job loss, but while they were still employed, delayed job loss.[47] Working conditions are potentially important modifiable risk factors. On this regard, Chorus *et al.*[48,49] found that individuals with rheumatoid arthritis who had received at least one form of workstation accommodation (included shortening work hours, slowing pace of work, changing tasks and being allowed to manage work) were 2.5 times less likely to be work disabled; but these interventions require further investigation and should be addressed to other prevalent and/or disabling rheumatic conditions as well. Also, Abásolo *et al.*[50] reported a successful case in which rheumatologists following detailed proceedings in a specialist-run early intervention program had an effect on work disability, at least for some forms of RD.

Although, there is already some amount of evidence on the effect of certain interventions on the likelihood of early departure from work attributable to RD, it is unquestionable the need to research further this topic. From a societal perspective, some of these interventions are likely to be cost-effective by providing long-term productivity gains, which should offset the investment costs in this crucial area. Our results underlines the high economic burden of RD coming from early retirement and offer useful background information to help prioritize investments in health and social protection policies targeting patients with rheumatic conditions.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- Data suggest a strong association between rheumatic diseases (RD) and likelihood of early exit from paid employment.
- There is a great potential concerning the risk reduction of early exit from work by eliminating or controlling rheumatic disorders in the population.
- Estimated indirect costs of early exit from work attributable to RD amounts to approximately 0.4% of the national GDP.
- Early retirement attributable to RD is therefore an important public health issue and its economic impact highlights the need for sustainable health policies.

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APPENDICES

Appendix 1 – Summary of average unit values of production by gender, age-group and geographic region

MEN								
Age-group	**National**	**North**	**Center**	**Lisbon**	**Alentejo**	**Algarve**	**Azores**	**Madeira**
50-54	€20 204	€16 712	€17 270	€27 673	€17 619	€17 085	€17 161	€22 562
55-59	€19 897	€16 491	€16 565	€27 697	€16 891	€17 714	€17 706	€21 002
60-64	€18 135	€16 499	€16 017	€25 282	€14 729	€17 460	€15 607	€17 045
Average (50-64)	€19 455	€16 568	€16 632	€26 935	€16 506	€17 424	€16 877	€20 472
WOMEN								
Age-group	**National**	**North**	**Center**	**Lisbon**	**Alentejo**	**Algarve**	**Azores**	**Madeira**
50-54	€13 579	€11 136	€10 528	€18 360	€11 872	€12 735	€12 344	€14 782
55-59	€13 137	€12 315	€10 766	€17 004	€11 446	€12 243	€12 350	€13 815
60-64	€11 863	€10 951	€13 145	€13 356	€9 263	€11 572	€11 157	€12 586
Average (50-64)	€12 899	€11 500	€11 571	€16 513	€10 975	€12 203	€11 980	€13 789

Appendix 2 - Logistic regression analysis by type of early exit from paid employment. [OR=Odds Ratio; 95% CI=95% confidence interval]

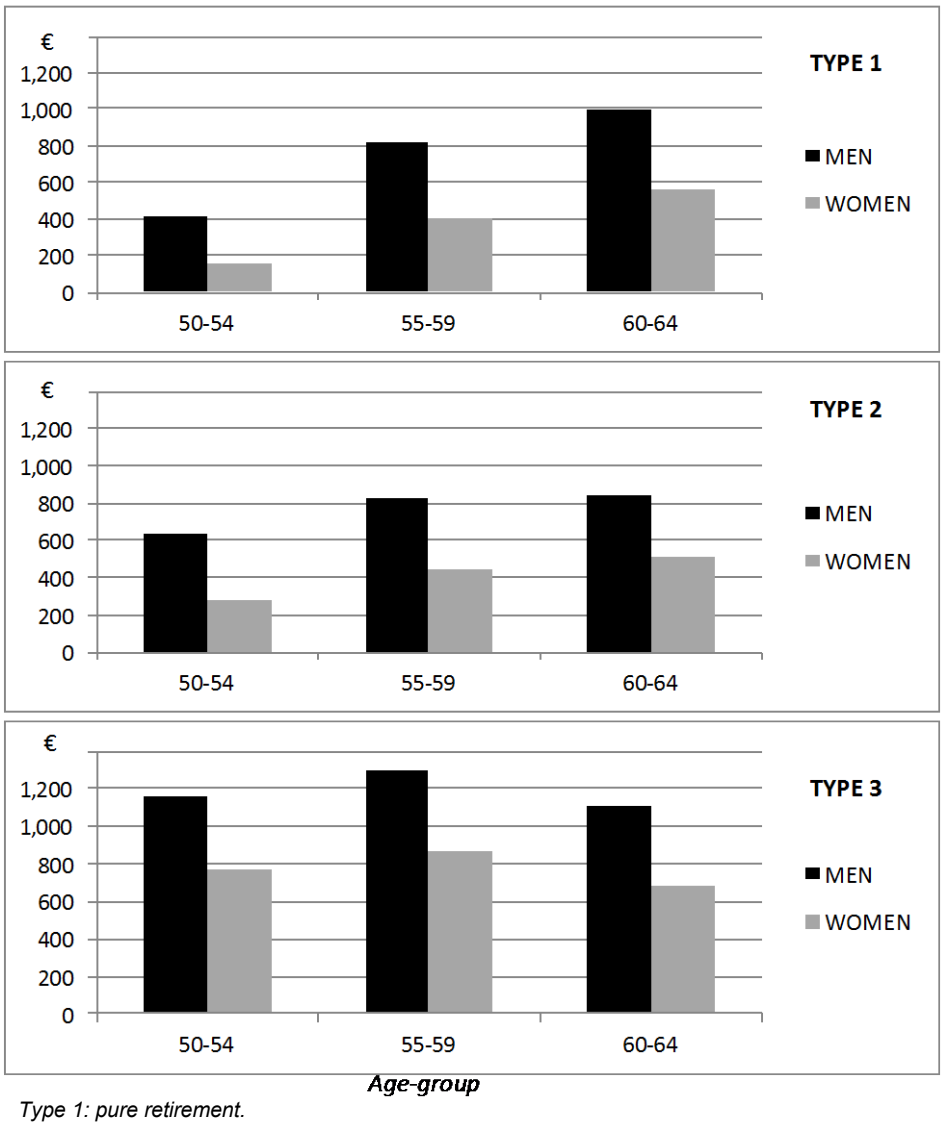
	TYPE 1 (EARLY RETIREMENT)		TYPE 2 (EARLY RETIREMENT + UNEMPLOYMENT)		TYPE 3 (EXIT FROM PAID EMPLOYMENT)*	
	Univariate Regression OR (95% CI)	*Multivariate Regression OR (95% CI)*	*Univariate Regression OR (95% CI)*	*Multivariate Regression OR (95% CI)*	*Univariate Regression OR (95% CI)*	*Multivariate Regression OR (95% CI)*
Rheumatic Diseases	1.36 (1.15-1.62)	1.24 (1.01-1.52)	1.22 (1.04-1.42)	1.20 (1.01-1.43)	1.62 (1.36-1.92)	1.31 (1.12-1.52)
Age						
50-54	1	1	1	1	1	1
55-59	3.19 (2.44-4.18)	3.27 (2.46-4.33)	2.06 (1.67-2.54)	2.11 (1.70-2.61)	2.13 (1.73-2.62)	1.86 (1.55-2.22)
60-64	8.79 (6.79-11.37)	9.97 (7.56-13.2)	4.20 (3.43-5.15)	4.44 (3.59-5.51)	4.79 (3.87-5.94)	4.32 (3.58-5.22)
Gender (Female)	0.61 (0.52-0.73)	0.54 (0.44-0.66)	0.61 (0.52-0.71)	0.56 (0.48-0.67)	2.12 (1.80-2.51)	*
Education						
Low	1	1	1	1	1	1
Medium	1.32 (1.05-1.65)	1.59 (1.22-2.08)	1.26 (1.02-1.55)	1.48 (1.18-1.85)	0.64 (0.50-0.82)	0.97 (0.78-1.20) NS
High	1.13 (0.89-1.44) NS	1.26 (0.91-1.75) NS	0.90 (0.72-1.14) NS	1.14 (0.89-1.45) NS	0.42 (0.33-0.55)	0.68 (0.52-0.89)
Household income						
≤€500	1	§	1	§	1	1
>€500 & ≤€900	0.99 (0.79-1.26) NS	§	1.03 (0.83-1.27) NS	§	0.68 (0.54-0.85)	0.84 (0.69-1.04) NS
>€900 & ≤€2000	1.18 (0.94-1.48) NS	§	1.06 (0.86-1.30) NS	§	0.58 (0.46-0.72)	0.78 (0.64-0.96)
>€2000	1.35 (1.01-1.78)	§	0.87 (0.66-1.13) NS	§	0.39 (0.29-0.53)	0.66 (0.48-0.89)
Comorbidities						
Asthma	1.57 (1.13-2.18)	1.61 (1.10-2.35)	1.37 (1.00-1.87)	§	1.70 (1.18-2.45)	§
Chronic pain	1.36 (1.14-1.63)	1.38 (1.12-1.70)	1.32 (1.11-1.56)	§	1.62 (1.34-1.94)	§
Cancer	1.94 (1.29-2.89)	2.00 (1.26-3.16)	1.69 (1.15-2.48)	§	1.48 (0.94-2.33) NS	§
Renal Impairment	3.36 (2.15-5.25)	2.96 (1.74-5.05)	2.95 (1.89-4.59)	2.60 (1.62-4.16)	2.87 (1.56-5.27)	§
Stroke	3.56 (2.24-5.66)	2.94 (1.72-5.03)	3.47 (2.18-5.51)	3.02 (1.85-4.95)	2.36 (1.34-4.16)	§
Area of residence						
North	1	1	1	1	1	1
Center	0.74 (0.59-0.94)	0.68 (0.53-0.88)	0.59 (0.48-0.73)	0.55 (0.44-0.68)	0.49 (0.39-0.61)	0.53 (0.43-0.64)
Lisbon	1.00 (0.81-1.25) NS	0.85 (0.67-1.09) NS	0.86 (0.71-1.05) NS	0.77 (0.62-0.95)	0.76 (0.61-0.95)	0.77 (0.63-0.94)
Alentejo	1.07 (0.86-1.34) NS	1.08 (0.85-1.38) NS	0.94 (0.77-1.16) NS	0.92 (0.74-1.14) NS	0.71 (0.56-0.89)	0.72 (0.58-0.88)
Algarve	0.73 (0.58-0.92)	0.67 (0.52-0.86)	0.62 (0.51-0.76)	0.57 (0.46-0.70)	0.61 (0.49-0.76)	0.62 (0.51-0.76)
Azores	0.85 (0.68-1.06) NS	0.83 (0.65-1.07) NS	0.56 (0.46 – 0.69)	0.54 (0.44-0.68)	0.94 (0.75-1.19) NS	1.04 (0.86-1.27) NS
Madeira	0.59 (0.44-0.78)	0.60 (0.44-0.82)	0.42 (0.33-0.55)	0.42 (0.32-0.56)	0.68 (0.53-0.86)	0.85 (0.68-1.07) NS

** Exit from paid employment includes: early retirees, unemployed, permanently disabled, homemakers, others.*

**Cofactor not included in the model (VIF>5).*

§ Cofactor excluded in the stepwise method (backward elimination with p>0.05).

Appendix 3 – Indirect Costs attributable to RD for different age-groups (by type of early exit from work and gender) per inhabitant with RD.



Type 1: pure retirement.
Type 2: pure retirement + unemployment.
Type 3: all forms of exit from paid employment

Article C: The Economic Impact of Early Retirement Caused by Rheumatic Diseases - Results from a Nationwide Epidemiologic Study

Pedro A. Laires, Miguel Gouveia, Helena Canhão, Jaime C. Branco

Public Health. 2016 Aug 12. pii: S0033-3506(16)30162-7.

Available online at www.sciencedirect.com

Public Health

journal homepage: www.elsevier.com/puhe

Original Research

The economic impact of early retirement attributed to rheumatic diseases: results from a nationwide population-based epidemiologic study

P.A. Laires [a,b,c,*], M. Gouveia [d], H. Canhão [c,e], J.C. Branco [c,e,f]

[a] Faculdade de Medicina da Universidade de Lisboa, Lisbon Academic Medical Center, Lisbon, Portugal
[b] Centro de Investigação em Saúde Pública, Escola Nacional de Saúde Pública, Lisbon, Portugal
[c] EpiReumaPt Study Group – Sociedade Portuguesa de Reumatologia, Lisbon, Portugal
[d] Catolica Lisbon School of Business and Economics, Lisbon, Portugal
[e] Chronic Diseases Research Center (CEDOC), NOVA Medical School, Universidade Nova de Lisboa (NMS/UNL), Lisboa, Portugal
[f] Rheumatology Department, Hospital Egas Moniz – Centro Hospitalar Lisboa Ocidental (CHLO-E.P.E.), Lisbon, Portugal

ARTICLE INFO

Article history:
Received 29 January 2016
Received in revised form
17 May 2016
Accepted 6 July 2016
Available online xxx

Keywords:
Early retirement
Exit from paid work
Years of working life lost
Work disability
Rheumatic diseases
Epidemiologic study
Population-based survey

ABSTRACT

Objectives: To measure early retirement due to self-reported rheumatic diseases (RDs) and to estimate the respective indirect costs and years of working life lost (YWLL).

Methods: We used individual level data from the national, cross-sectional, population-based EpiReumaPt study (September 2011–December 2013) where 10,661 inhabitants were randomly surveyed in order to capture and characterize all cases of RD within a representative sample of the Portuguese population. In this analysis, we used all participants aged between 50 and 64 years, near the official retirement age. A national database was used to calculate productivity values by gender, age and region, using the human capital approach. YWLL were estimated as the difference between each participant's current age and the respective retirement age, while the potential years of working life lost (PYWLL) were given by the difference between official and actual retirement ages. We also calculated the percentage of time in inactivity (inactivity ratio = YWLL/Active age-range [15–64 years old]).

Results: 29.9% of the Portuguese population with ages between 50 and 64 years were retired with 13.1% self-reporting retirement due to RD. The estimated annual indirect cost following premature retirement attributed to RD was €910 million (€555 per capita; €1625 per self-reported RD patient and €13,592 per early retiree due to RD). Females contributed with 84% for these costs (€766 million; €882 per capita vs €187 from males). We observed a

* *Corresponding author*. Sociedade Portuguesa de Reumatologia, Av. de Berlim, 33 B, 1800-033, Lisbon, Portugal.
E-mail address: laires.pedro@gmail.com (P.A. Laires).

http://dx.doi.org/10.1016/j.puhe.2016.07.004

total number of 389,939 accumulated YWLL (228 per 1000 inhabitants) and 684,960 PYWLL (401 per 1000 inhabitants). The mean YWLL and PYWLL inactivity ratios were 12% and 21%, respectively. RD patients with higher values of disability have the highest risk of early retirement.

Conclusions: Early retirement attributed to self-reported RD amounts to approximately 0.5% of the national gross domestic product (GDP) in 2013, due to large YWLL. Both the public health concern and the economic impact highlight the need to prioritize investments in health and social protection policies targeting patients with rheumatic conditions.

Introduction

Early retirement generates a serious problem for social and economic sustainability in developed countries where, in recent decades, there has been a substantial rise in the percentage of the labour force out of work because of sickness or disability and in the related social protection benefits.[1,2] The combination of an ageing population and widespread early retirement puts severe strains on our social security systems' capacity to maintain today's standard of living for future generations of older people. In particular, Portugal is already among the oldest countries in the world, with one of the highest old-age dependency ratios, and it is in the forefront of this general concern regarding premature work withdrawal.[2] Early retirement is influenced by several factors, including progressively prevalent chronic pathologies, such as rheumatic diseases (RD).[3–15,40] RD are among the most common chronic non-communicable diseases. They are the leading cause of work disability in developed countries and consume a large amount of health and social resources,[16–18] where over a third of the population approaching the statutory retirement age suffers from some type of RD.[19–21] This situation is expected to deteriorate in the coming future, and therefore, RD is expected to cause growing productivity losses (indirect costs), in particular by premature departures from the labour market. Thus, better knowledge about the relationship between RD, its functional limitations and the ability to work is fundamental to prevent early retirement. Moreover, measurement of current indirect costs of RD may raise awareness on public opinion and decision makers, ultimately triggering needed action.

Previous research has measured this sort of indirect costs, but mostly addressed specific rheumatic conditions or used data from broad non-specific surveys.[4,5,12,22–27] Given the importance and the aforementioned impact of this topic, it is also relevant to explore it with RD-specific information, namely disability data and direct subjects' reports on the occupational impact caused by these diseases as a whole.

Thus, the main aim of this study is to measure early retirement attributed to self-reported RD, the respective indirect costs and years of working life lost, based on a nationwide RD-specific survey, which directly addressed the occupational impact due to these health conditions.

Methods

Sample

This study uses the first national, cross-sectional, population-based study on RD in all regions of Portugal – EpiReumaPt study. The methodology of EpiReumaPt has been detailed elsewhere.[28] Briefly, EpiReumaPt (September 2011–December 2013) randomly selected 10,661 adult subjects through a stratified multistage sampling by Portuguese regions (European NUTS II level) and by size of location. Participant households were selected by the random route methodology. Face-to-face interviews inquired participants about socio-demographic data, socio-economic profile (measures of wealth, household income, current professional status), life style (e.g. alcohol and coffee intake), anthropometric data (weight and height), quality of life (European Quality of Life questionnaire with five dimensions and three levels validated for Portugal, EQ-5D index[29,30]) functional capacity (Health Assessment Questionnaire, HAQ[31]), and self-reported chronic non-communicable diseases, including RD. Additionally, EpiReumaPt has data on the economic impact of RD, such as healthcare consumption (number and type of medical appointments, hospitalizations, homecare assistance and other healthcare service's needs, in the previous 12 months), early retirement, disability pensions and other forms of premature withdrawal from work.

For the purposes of this analysis, we used data from the first phase of EpiReumaPt for all participants from Portugal mainland aged between 50 and 64 years old near the official retirement age of 65 years (1065 men and 1727 women). The sample was considered representative of the Portuguese population.[28,32]

Measurements

For this analysis, we considered the presence of RD through self-reporting. The same applies for the following major chronic diseases: diabetes, cardiovascular disease (including risk factors such as hypertension and high cholesterol), allergy, pulmonary disease, gastrointestinal disease, neurological disease, mental disease and cancer. A proxy measure of general morbidity was built as the sum score of all aforementioned chronic illnesses (comorbidity score). Obesity was measured according to the body mass index (underweight: $<18.5\ m^2/kg$, normal: $18.5–25\ m^2/kg$, overweight: $25–30\ m^2/kg$,

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obese: ≥30 m^2/kg). Area of residence was defined according to the regional location of each household (North, Center, Lisbon, Alentejo and Algarve). Marital status variable was classified by five categories (single, married, consensual union, divorced and widowed). Educational level was grouped into three major levels according to the highest degree completed: low (primary school or less), medium (basic education between primary and secondary levels) and high (secondary education or more, including university degrees).

Years of working life lost (YWLL) and inactivity ratio

YWLL were determined for cases with premature retirement attributed to RD estimated as the difference between each participant's age at the time of the survey and the respective retirement age, while the potential YWLL (PYWLL) is the difference between official and actual retirement ages. PYWLL assumes there is no return to work. We also calculated the percentage of time in inactivity by dividing each early retiree YWLL and PYWLL by the active age range of 15–64 years old (inactivity ratio = YWLL and PYWLL/active age range). We reported the mean inactivity ratios for the whole population of early retirees due to RD.

Indirect costs

Early retirement due to RD was primarily assessed through participants' self-reporting ('Did you retire due to RD?'). In order to calculate the corresponding indirect costs of such economic impact, we adopted society's perspective and used the human capital approach to estimate productivity costs by valuing healthy time lost due to the disease using market wage rates, which can be viewed as the loss of an investment in a person's human capital.[33]

The value of lost production was assessed by obtaining the mean market wages (fixed and variable portions of compensation) from national public sources for 2013.[34] These figures needed to be adjusted for social security contributions since the economic cost of lost production is based on total costs to employers. This approach yielded an annual average value of €24,891 for men and €16,079 for women, for ages between 50 and 64 years. All unit values of lost production were stratified by age, gender and geographic region (Appendix 1).

Annual indirect costs associated with early retirement due to RD were obtained by summing all annual average values of production (assigned in the EpiReumaPt sample according to age, gender and region) for those who self-reported early retirement due to RD.

The methodology described above may overestimate indirect costs by not considering additional retirement risks imposed by other factors. To correct for that possibility, we also deployed population attributable fractions (PAF). PAF were calculated as the resulting proportional change in the probability of early retirement due to RD (using logistic multivariable models explaining retirement) after a counterfactual exercise where the presence of RD is artificially eliminated from the sample. This recalculated probability of early retirement was then used to estimate the indirect costs attributable to RD by multiplying each observation's change in the probability of retirement with the corresponding unit value of production.

Statistical analysis

Descriptive analysis was mainly performed comparing retired against non-retired individuals. Prevalence of retirement and other characteristics were computed weighting the data, in order to take into account the sampling design of the survey. Missing values were not replaced, and all statistics were calculated based on non-missing values. In this survey, respondents were directly asked if their early retirement was due to a RD. However, since these disorders may underlie and contribute for early retirement even when RD is not self-reported to be its cause, we also measured the association between RD and overall early retirement through multivariable logistic regressions.

The logistic multivariable models were built by means of a manual stepwise technique (backward elimination), and only cofactors statistically significantly associated with the dependent variable ($P < 0.05$) were considered. All statistical analyses were carried out using Stata 12.0.

Results

Based on the inference from the sample to the total mainland Portuguese population at the time of this survey, 29.9% of the Portuguese population with ages between 50 and 64 years were retired and 52% were out of the labour force (including unemployment, disability pensions and any other form of exit from work). Among the early retirements, 43.2% were on grounds of ill health (12.9% of the overall sample), of which in turn about a third (30.4%) was specifically due to RD (Table 1). Thus, 13.1% of all retirees and 3.9% of the Portuguese population within the studied age-range self-reported RD as the main reason for early retirement. Of the population under study, 48% was employed. This subpopulation had higher levels of education, was less frequently married, less obese and had a lower number of chronic diseases compared with participants out of work, in particular those early retired due to RD (Table 1). Employed people also have less RD than the overall population and than the early retirees (30.0% vs 34.2% and 40.2%, $P < 0.001$ and $P = 0.017$, respectively). They had higher household income, with a lower presence in bottom salary ranges (i.e. <750€/month) while the opposite in the upper ones (i.e. >2000€/month). The majority of the early retirement attributed to RD was observed in females (81.6% vs 41.5% of females in the early retirement group not due to RD). As expected, the cumulative probability of this sort of early exit from work increases with age, in particular above the age of 50 years (Fig. 1).

Healthcare resource consumption

Those who self-reported RD also notified more healthcare consumption. The proportion of users and the mean number of medical hospital specialty appointments per user was higher (62.1% and 5.2 vs 51.4% and 3.4 for non-RD population, Appendix 2) as was the proportion of hospitalizations and home care assistance in the previous 12 months, although

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Table 1 – General description of the sample by employment status: EpiReumaPt ages 50–64 years ($n = 2792/N = 1,706,749$).

	No early retirement	Early retirement[a]	Early retirement due to disease[b]	Early retirement due to RD[c]	Paid employment	Early exit from paid employment[d]
Employment status	70.1%/1,195,906	29.9%/510,843	12.9%/220,489	3.9%/66,953	48.0%/819,137	52.0%/887,612
Age (years)	55.5	60.0 ($P < 0.0001$)	58.7 ($P < 0.0001$)	60.5 ($P < 0.0001$)	55.1	58.4 ($P < 0.0001$)
Gender (female)	55.7%	46.8% ($P = 0.02$)	52.4% ($P = 0.90$ NS)	81.6% ($P < 0.0001$)	51.4%	54.6% ($P = 0.32$ NS)
Educational level						
Primary or less	50.9%	61.6%	71.0%	83.3%	43.7%	63.6%
Medium	22.9%	19.7%	21.2%	10.2%	24.3%	19.8%
High	26.3%	18.7% ($P = 0.01$)	7.8% ($P = 0.0004$)	6.6% ($P < 0.0001$)	32.0%	16.6% ($P < 0.0001$)
Marital status						
Single	9.9%	6.3%	9.7%	4.5%	10.7%	7.1%
Married	68.8%	73.2%	64.4%	82.9%	68.6%	71.5%
Divorced	13.2%	11.0%	14.5%	3.9%	12.9%	12.2%
Widowed	6.4%	7.9%	9.2%	7.9%	6.3%	7.3%
Consensual union	1.7%	1.4% ($P = 0.21$ NS)	2.3% ($P = 0.62$ NS)	0.9% ($P = 0.08$ NS)	1.5%	1.7% ($P = 0.37$ NS)
Body mass index						
Underweight	0.6%	0.9%	1.0%	—	0.3%	1.0%
Normal	31.5%	27.5%	27.1%	21.5%	33.0%	27.7%
Overweight	43.6%	39.8%	34.2%	23.0%	46.0%	39.1%
Obese	24.4%	31.9% ($P = 0.10$ NS)	37.6% ($P = 0.05$)	55.5% ($P = 0.001$)	20.7%	32.2% ($P < 0.0001$)
Functional capacity—HAQ (0–3)	0.29	0.44 ($P = 0.0001$)	0.69 ($P < 0.0001$)	0.94 ($P < 0.0001$)	0.22	0.44 ($P < 0.0001$)
Quality of life—EQ-5D index	0.80	0.75 ($P = 0.004$)	0.66 ($P < 0.0001$)	0.59 ($P < 0.0001$)	0.84	0.75 ($P < 0.0001$)
Chronic diseases (self-reported)						
RD	31.7%	40.2% ($P = 0.03$)	49.7% ($P = 0.0007$)	84.9% ($P < 0.0001$)	30.0% ($P = 0.02$)	38.2%
Cardiovascular	58.2%	67.8% ($P = 0.007$)	75.8% ($P < 0.0001$)	77.2% ($P = 0.02$)	56.0%	65.9% ($P = 0.001$)
Diabetes	9.8%	17.6% ($P = 0.0001$)	22.3% ($P = 0.0002$)	23.5% ($P = 0.13$ NS)	7.9%	16.1% ($P < 0.0001$)
Pulmonary	4.9%	8.4% ($P = 0.04$)	10.6% ($P = 0.003$)	6.8% ($P = 0.75$ NS)	4.3%	7.5% ($P = 0.01$)
Allergy	20.9%	21.9% ($P = 0.75$ NS)	24.1% ($P = 0.45$ NS)	39.8% ($P = 0.04$)	20.9%	21.5% ($P = 0.77$ NS)
Gastrointestinal	18.8%	28.5% ($P = 0.003$)	32.6% ($P = 0.002$)	28.8% ($P = 0.26$ NS)	17.4%	25.7% ($P = 0.004$)
Neoplastic	3.8%	5.4% ($P = 0.15$ NS)	7.6% ($P = 0.02$)	3.0% ($P = 0.51$ NS)	3.5%	5.0% ($P = 0.12$ NS)
Mental	17.3%	24.9% ($P = 0.02$)	42.7% ($P < 0.0001$)	49.7% ($P = 0.0002$)	15.5%	23.4% ($P = 0.0009$)
Neurologic	2.3%	6.2% ($P < 0.0001$)	11.1% ($P < 0.0001$)	4.4% ($P = 0.62$ NS)	1.9%	5.0% ($P = 0.0001$)
Comorbidity score	1.68	2.21 ($P < 0.0001$)	2.77 ($P < 0.0001$)	3.2 ($P < 0.0001$)	1.57	2.08 ($P < 0.0001$)

RD, rheumatic diseases; HAQ, Health Assessment Questionnaire; EQ-5D, European Quality of Life questionnaire with five dimensions and three levels; NS, non-significant.

[a] P-values vs no early retirement.

[b] P-values vs no early retirement due to disease.

[c] P-values vs no early retirement due to RD.

[d] P-values vs employed.

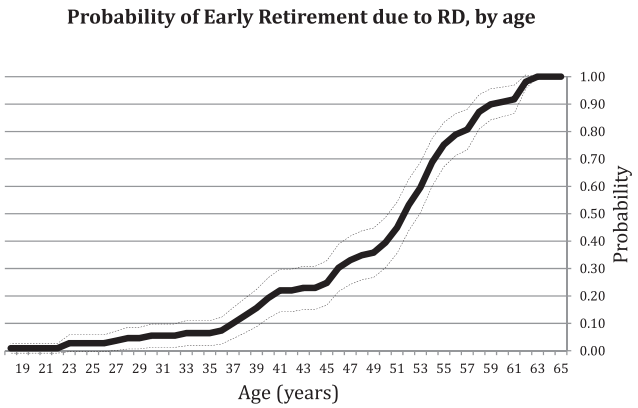

Fig. 1 – Probability of early retirement due to RD, by age. The confidence interval consists of the space between the two dashed lines. RD, rheumatic diseases.

non-statistically significant (12.8% and 1.5% vs 8.8% and 1.2% for non-RD population, Appendix 2). Among those self-reporting RD, 2.5% were hospitalized specifically due to RD in the same time period. On the other hand, 14.4% of early retirees were hospitalized vs 8.4% of non-retirees ($P = 0.03$).

RD and early retirement are associated with a higher number of medical appointments, and early retirement is associated with a higher likelihood of hospitalization (odds ratio [OR]: 1.84; confidence interval [CI]: 1.04–3.25; $P = 0.035$).

Association between RD and early retirement

More than a third (34.2%; females: 46.3%) of the studied population self-reported RD, being also more likely to self-report other main chronic disease (OR: 3.4; CI: 2.53–4.65; $P < 0.001$). Self-reported RD is independently associated with

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early retirement (unadjusted OR: 1.45; CI: 1.05–2.01; $P = 0.025$. Adjusted OR: 1.37; CI: 1.01–1.84; $P = 0.042$. Appendix 3). Some other characteristics are also associated with early retirement, in particular being older, being male and having other chronic diseases, specifically gastrointestinal and neurological diseases (Appendix 3). Additionally, higher levels of disability measured by the HAQ score increase the likelihood of early retirement (OR: 1.58; CI: 1.27–1.97; $P < 0.001$). On the other hand, the self-reported RD population has more disability with higher mean scores of HAQ (0.57 vs 0.21 for non-RD population, $P < 0.001$) and early retirees with RD have significantly worst score vs those with RD but not retired (0.69 vs 0.51, respectively; $P = 0.023$). The individuals with RD and higher levels of disability (i.e. HAQ scores ≥2) are at the utmost risk of early retirement (55.3% vs 35.1% for all RD population and 31.9% for those with HAQ scores ≥2 but without RD). Likewise, the highest association was measured between RD plus high disability and early retirement (adjusted OR: 3.87; CI: 1.63–9.16; $P = 0.002$. By contrast, non-significant adjusted ORs of 1.13 and 1.22 were obtained when testing the association of RD with early retirement in individuals with low disability measured by HAQ scores of <1 and <2, respectively). We estimated an almost linear relationship between levels of disability and the probability of early retirement, with its y-intercept and slope being increased by RD (Fig. 2).

Mean age of early retirement, YWLL and inactivity ratio

The observed mean age of early retirement attributed to RD was 54.8 years old. Despite the considerable variation throughout the years, there was an overall positive trend in the recent past (Fig. 3). Considering only those who retired prematurely in the last five years, the mean age of retirement due to RD is 58.2 years old and, projecting this trend over time, by year 2050, this figure could reach 65 years.

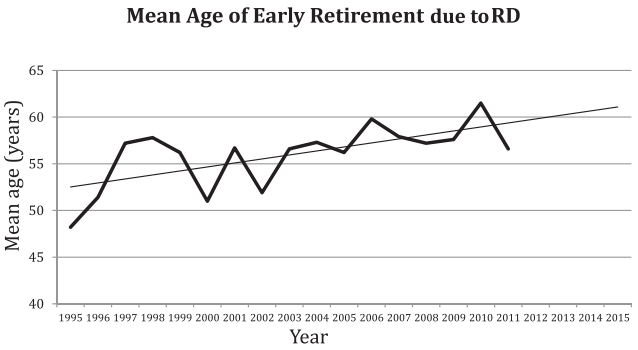

Fig. 3 – Evolution of mean age of retirement due to self-reported RD. RD, rheumatic diseases.

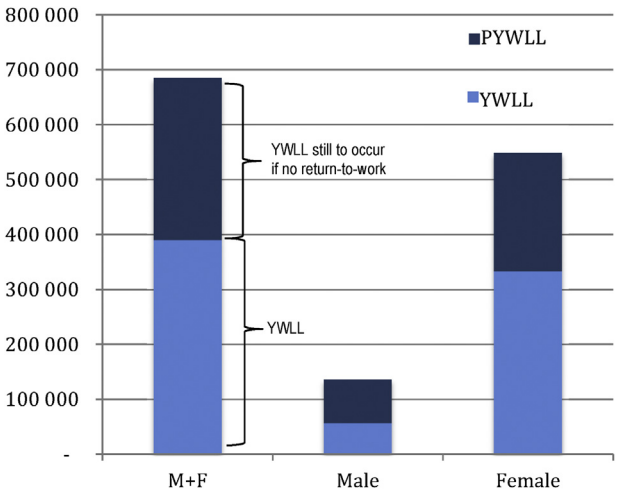

Fig. 4 – Years of working life lost due to self-reported RD. RD, rheumatic diseases; YWLL: years of working life lost; PYWLL: potential years of working life lost.

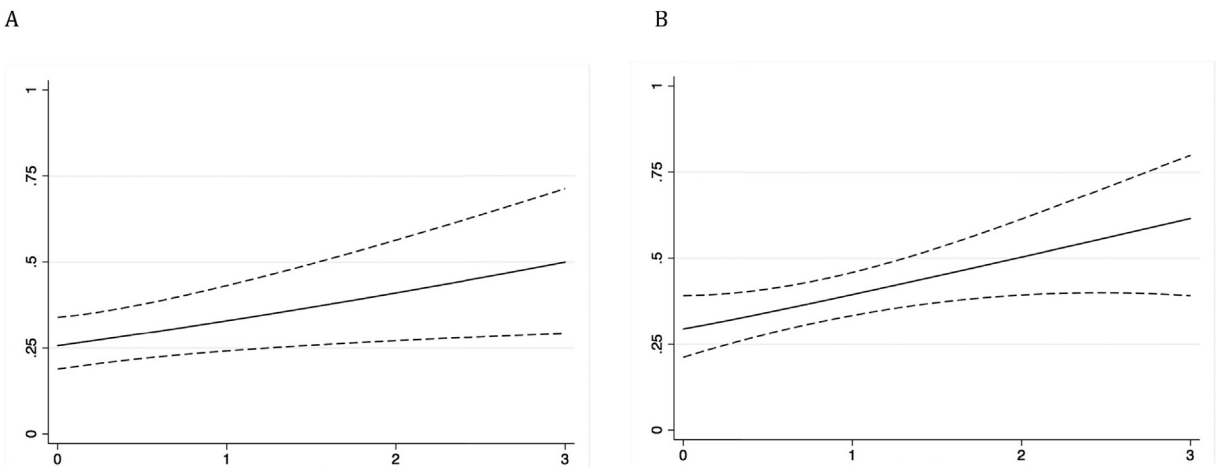

Fig. 2 – Relationship between disability levels and probability of early retirement (by presence of self-reported RD). Y-axis: probability of early retirement; X-axis: disability level measured by the HAQ Score. (A) Without self-reported RD; (B) With self-reported RD. The confidence interval consists of the space between the two dashed lines. RD, rheumatic diseases; HAQ, Health Assessment Questionnaire.

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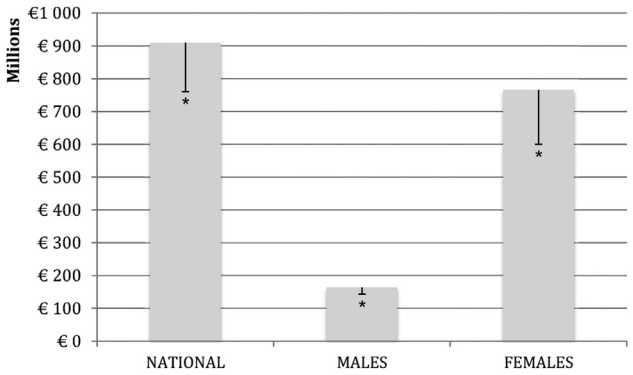

Fig. 5 – Annual indirect costs of early retirement due to self-reported RD. *Line inside bars refers to the lowest estimate. RD, rheumatic diseases.

Urban regions seem to be associated with higher mean age of early retirement attributable to RD.

This sort of early retirement has led to a total of 389,939 YWLL (228 per 1000 inhabitants). Women accounted for 85% of these YWLL. A total number of 684,960 PYWLL were estimated (401 per 1000 inhabitants) (Fig. 4). The mean YWLL and PYWLL inactivity ratios were 12% and 21%, respectively.

Indirect costs

The estimated annual indirect cost following premature retirement attributed to RD was €910 million (€555 per capita; €1625 per self-reported RD patient and €13,592 per early retiree due to RD). Females contribute with 84% of these costs (€766 million; €882 per capita vs €187 for males—Figs. 5 and 6). Moreover, we estimated a mean global cost of €117,502 (95% CI: €78,171–€156,832) per early retiree due to RD from each one's actual age of retirement until the 65 years official age of retirement (assuming a constant annual productivity values for past years and applying an annual 5% discounting rate for future years as recommended by our national health economics guidelines).[35] The global mean past cost per early retiree due to RD was €67,569 (95% CI: €43,467–€91,670), while the mean global future discounted costs if no return to work occurs is expected to be €48,304 (95% CI: €29,025–€67,582).

Finally, after using the PAF methodology, due to the reasons already explained, the overall indirect costs reduced by approximately 16% (i.e. €761 million, €464 per capita and €1359 per self-reported RD patient).

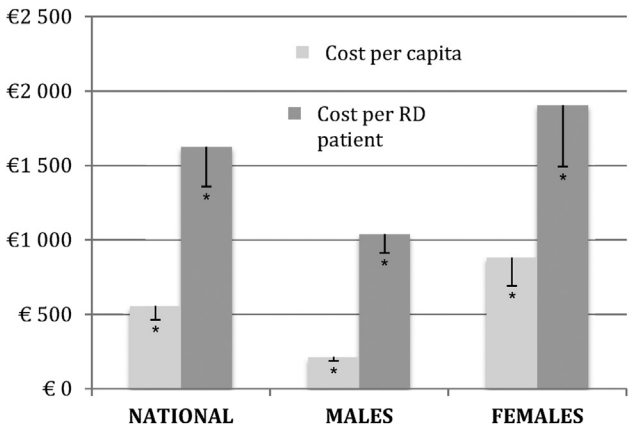

Fig. 6 – Annual indirect costs of early retirement due to self-reported RD (per capita). *Line inside bars refers to the lowest estimate. RD, rheumatic diseases.

Discussion

In this research, after implementing the first large-scale epidemiological population-based study that evaluated RD in Portugal, we estimated that early retirement self-reportedly to be due to RD is potentially associated with an annual cost of up to €910 million in Portugal. These pathologies are highly frequent in the population, especially among the oldest. In our sample, we observed a proportion of over a third of self-reported RD, and among these, a third was retired and more than half were non-employed. There is a noticeable network of factors influencing retirement decisions, and many factors are both related with RD and early retirement, including age, comorbidities, income and educational level. However, we found the association with self-reported RD to be robust and independent from other influencing factors, and this is consistent with previous published data.[3,13,36] In fact, we observed a high number of accumulated YWLL and substantial inactivity ratios attributed to RD, which translates into the abovementioned costs for society—approximately 0.5% of the national gross domestic product (GDP) in 2013. This considerable economic burden has been observed in other countries.[37–41] For instance, in Australia, arthritis caused an annual estimated loss of approximately 0.7% of GDP due to early retirement.[42]

The EpiReumaPt study collected a considerable amount of data, including occupational and socio-economic variables. The specific sample used in this survey had ages in the vicinity of the statutory retirement age, and more than half were out of paid work meaning that substantial productivity losses were occurring, in particular due to ill health. These results are in line with previous research using data from the Portuguese Health National Survey 2005/2006 (INS),[15] meaning that no improvements have been made since then at the epidemiological level (i.e. similar prevalence of self-reported RD—INS: 37.2% vs EpiReumaPt: 34.2% and similar association with early retirement—adjusted ORs were: 1.24 in the INS vs 1.37 in EpiReumaPt). In fact, from a strictly economic perspective, this situation may have worsened. At the time of INS 2005/2006, we estimated a productivity loss due to RD of up to €650 millions, amounting up to 0.4% of GDP. This difference may result from several reasons, including higher productivity unit values (INS 2005/2006, men: €19,455 women: €12,899 vs EpiReumaPt 2011/2013: men: €24,891 women: €16,079) and methodological differences (e.g. in the EpiReumaPt study participants were for the first time directly

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asked whether they had had retired early because of RD). From the epidemiological and clinical standpoints, there's no reason to expect the aforementioned difference. In fact, as discussed, we measured similar self-reported prevalences and there's no reason to expect any recent increase in the frequency of more disabling types or worst stages of RD. Finally, we also do not anticipate any sort of survivorship bias (survival of the fittest) effect because there is no significant RD-specific mortality, in particular within the studied age range, meaning that no imbalance is expected between both analysis concerning the most vulnerable RD subjects. Obviously, many other reasons may play important roles, including occupational and organizational ones. Changes in the retirement policies are expected to have an impact as well. Recently, early retirement was subjected to more restrictive rules (e.g. more rigorous screening of applicants to disability pensions lead to younger applicants having lower probabilities of success), but on the other hand, many applicants anticipated their decisions of early withdrawal from work in order to avoid expected future penalties and worse eligibility criteria for retirement. It is difficult to understand exactly the magnitude of these opposing structural effects, in particular for the RD population, but definitely the recent sovereign debt crisis and subsequent social reforms must have had considerable influence. It is also arduous to predict its evolution; however, despite the already discussed changes, we observed a positive trend on the mean age of early retirement attributed to RD. A lot remains to comprehend about the undermining reasons of this trend. For instance, if early retirement caused by RD is artificially postponed (e.g. excessive penalties unaffordable for those with lower income) or instead if structural policies are taking place to avoid RD disability and promote job adaptation. Obviously, any measure that obligates the labour force to employ the same effort under the same conditions regardless its physical and functional circumstances may adjourn indirect costs in the short run, but would not work on the longer one and even may exacerbate medical conditions leading to higher direct costs.

In this study, we observed higher healthcare consumption in the RD population, which in turn translates into higher direct costs. The hospitalization and medical appointments rates were higher compared to the non-RD population. Interestingly, early retirement was also associated with these costs. This might be due to a general worsening of health prior to retirement or instead triggered/worsened by it. If the last case is true, permissive criteria concerning disability pensions and early retirement *per se* does not guarantee any cost offset from less healthcare consumption.

At a global level, occupational policies have focused on job retention rather than on the return to work.[43] Although we recognize that return-to-work policies are less likely to be successful, we also need to highlight that our data suggest that they would provide significant productivity gains to society. In this sample, we measured 389,939 YWLL and expect a similar number of YWLL from the same individuals until the official retirement age. Therefore, if nothing is done, otherwise, the amount of working years still to be lost from the current early retirees due to RD will almost equal those already gone, meaning that health policies probably should target return to work as well, in particularly for younger retirees. It is true that RD are degenerative and progressively disabling, but is also true that there is a growing number of interventions available to reduce and control physical impairment, which allied with vocational rehabilitation and job accommodation (e.g. ergonomic adaptations) might allow some RD patients to return to work.

In general, the data show that women are less prone to early retirement. However, the opposite occurs when the cause is RD. Currently, females contribute with about 85% of YWLL and indirect costs attributed to RD. Since RD is more prevalent in women, it is not surprising that YWLL and indirect costs split by gender are unbalanced with greater burden on females. In addition, we also observed more disability in females among those self-reporting RD (data not shown), which might contribute to this gender difference in our results, given the straightforward relationship between disability and early retirement due to RD. Sadly, in the last decade, we did not observe any trend to reduce wage disparities between genders in the age-range studied (compound annual growth rate for men is 3.1% while it is 2.8% for women). If gender wage disparities had been reduced, the estimated indirect costs would have been even higher. In fact, if we were to assume productivity values similar to those of men for the whole sample, the indirect costs estimate would rise by about 30%. Future research is necessary to understand how these costs will evolve in the coming years as a function of the expected evolution of gender disparities.

We also observed a strong association between high scores of HAQ and early retirement. Within the model of the aetiology of work disability (Pathology—Impairment—Functional Limitations—Work Disability—Early Retirement),[44,45] HAQ might be a good proxy to detect risk of health-related premature retirement. In this context, early retirees with RD have significantly worst HAQ values compared to individuals still at work under the same clinical conditions, and there is a cumulative risk of early retirement when the RD patient already has high levels of HAQ. This means that it might be worthwhile to segment RD patients according with disability levels because that is a straightforward method to set distinct levels of work withdrawal risk. Targeting RD as a whole regardless of any other factor might be an approach too broad to be effective. Since HAQ assessment is simple and inexpensive, employers could periodically survey employees regarding ill-health conditions, including RD, and their disability level. This could be a fruitful proactive investment particularly for manual workers.

This analysis is based on self-reported data, meaning that from a rigorous epidemiological angle, this research might be subject to misclassification bias (i.e. main independent variable not clinically confirmed). In fact, we grouped all participants who did not self-reported RD in the non-RD population, but many might suffer from a rheumatic condition. However, these results should also be used from a pragmatic angle to encourage fast and easy

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identification of vulnerable employees according with their level of retirement risk. Certainly, all cases of self-reported RD must be clinically confirmed (in order to avoid false claims and misperception about self-conditions), but this proxy might not only be easier to obtain but also more useful compared with a broader RD clinical diagnosis since the strong correlation between disease self-awareness and worst/advanced disease stages (i.e. higher disability and therefore early retirement risk). In addition, given the recognizable low access to specialist appointments that some population segments still have, self-reported information about RD should be considered prior to further and more complex measures (including upfront diagnosis assessment and possible customized interventions).

We do not expect our results to be influenced by justification bias (i.e. some people may want to justify their early retirement through health problems, which is a common limitation in this type of research).[46] The EpiReumaPt questionnaire is not exclusively dedicated to occupational data, and the survey did not generate any sort of pressure for responders to justify their retirement condition. Nevertheless, some limitations must be taken into account when interpreting the results of this study. First, it may be limited by its cross-sectional design, which does not allow for an evaluation of the temporal relationship between some cofactors and the studied outcomes. However, in order to calculate the indirect costs, we used data mainly from the direct question about early retirement due to RD. The same was done regarding date and age of early retirement attributed to RD. Thus, for the main objectives of this work, we do not expect any temporal bias (also known as reverse causality) from this study design. However, the reported age of early retirement is still subject to memory bias. Second, the human capital method has been criticized for its overestimation of indirect costs[47] since the real paid production loss to society is likely to be lower (for instance, the work can be done by someone drawn from the unemployment pool). The friction cost approach has been proposed as an alternative to calculate indirect costs; however, it is considered less appropriate to estimate the productivity losses for early retirees, which was the focus of our research.[47–49] On the other hand, unit values of production were estimated through official statistics based on gender, region and age. Necessarily, this methodology is a rough estimate of individual unit values of production. In particular, RD patients are associated with lower incomes. Still, given the information available, it is the most suitable method. Third, RD may underlie early retirement even when it is not perceived by the patient, and our indirect costs calculation might have been undervalued because it did not consider other forms of RD contribution to premature withdrawal from work (e.g. by triggering or worsening another cause of early retirement, such as associated comorbidity, lifestyle and sociodemographic conditions). Finally, due to the cross-sectional design, our results are right-censored, leading to likely underestimation of the results (i.e. early retirement more probable to occur than return to work within the sample until all participants reach the official retirement age).

This study has several strengths too. It is the first population-based study on RD in our country, allowing direct information between RD and its occupational impact. To our knowledge, this must be among the few studies focusing on indirect costs based on a representative sample specifically dedicated to RD. Moreover, this database will allow prospective follow-up to better understand the various paths of early retirement and its connection with RD and other factors in more detail.[50] It will also allow future research on the effectiveness of interventions targeting early retirement.

To conclude, this comprehensive population-based research underlines the high economic burden of RD concerning early retirement, justifying more attention when discussing policies facing one of the most relevant sustainability issues of ageing western countries. Rheumatic disorders are still undervalued in health policies. However, we cannot afford to be inactive regarding this topic any longer and should address possible interventions intended to mitigate early retirement attributed to RD (e.g. early diagnosis, effective treatment and vocational rehabilitation).[51] The depreciation in the stock of human capital due to self-reported RD through early retirement already amounts to approximately 0.5% of the national GDP, and given the demographic and epidemiologic trends, it might get even higher if nothing is done otherwise. Therefore, public health policies must indeed directly address this sort of foregone productivity with effective strategies, which ultimately aim to improve patients' quality of life and the wealth of our society. This research provides a strong case to move fast on this direction with relevant evidence for decision makers to prioritize investments in health and social protection policies targeting patients with rheumatic conditions, in particular those highly disabled.

Author statements

Acknowledgements

The authors would like to acknowledge the invaluable help of all rheumatologists and investigators who contributed to the EpiReumaPt study, in particular Ana Rodrigues, MD; Nélia Gouveia, PharmD PhD; and Mónica Eusébio, MSc. The authors would also like to acknowledge the EpiReumaPt external consultants: João Eurico da Fonseca, MD PhD; Loreto Carmona, MD PhD; Henrique de Barros, MD PhD; and José António Pereira da Silva, MD PhD.

Ethical approval

EpiReumaPt study was performed according to the principles established by the 1964 Helsinki declaration and its later amendments and according to the Portuguese law. EpiReumaPt was reviewed and approved by competent Portuguese authorities: NOVA Medical School Ethics Committee and National Committee for Data Protection. The study was also reviewed and approved by the Ethical Committees of Regional Health Authorities.

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Funding

None declared.

Competing interests

None declared.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Appendix 1. Summary of average unit values of production by gender, age and geographic region (2013).

Age	National	North	Centre	Lisbon	Alentejo	Algarve
Men						
50	€22,868	€21,271	€21,091	€32,376	€21,147	€19,808
51	€23,875	€21,066	€20,753	€32,081	€21,659	€18,518
52	€24,609	€21,357	€20,290	€31,991	€22,772	€19,523
53	€24,688	€21,497	€20,834	€32,895	€22,182	€18,722
54	€25,831	€21,942	€20,475	€31,422	€24,079	€19,314
55	€25,624	€22,005	€21,086	€32,877	€23,712	€20,063
56	€25,185	€22,005	€21,065	€33,006	€24,686	€18,943
57	€25,813	€22,665	€20,187	€33,248	€23,917	€20,398
58	€23,696	€22,757	€20,719	€34,349	€24,228	€18,808
59	€25,881	€23,593	€21,222	€34,765	€25,096	€20,406
60	€23,843	€21,586	€20,037	€32,585	€24,078	€19,509
61	€26,350	€22,616	€21,393	€36,334	€22,330	€19,943
62	€25,966	€24,180	€20,432	€34,934	€25,275	€18,210
63	€24,645	€23,053	€19,851	€33,056	€25,360	€17,408
64	€24,490	€24,474	€20,181	€34,764	€28,163	€17,266
Average (50–64)	€24,891	€22,404	€20,641	€33,379	€23,912	€19,123
Women						
50	€16,290	€14,524	€13,384	€20,811	€13,740	€15,466
51	€15,880	€14,864	€13,451	€20,522	€13,811	€15,637

Please cite this article in press as: Laires PA, et al., The economic impact of early retirement attributed to rheumatic diseases: results from a nationwide population-based epidemiologic study, Public Health (2016), http://dx.doi.org/10.1016/j.puhe.2016.07.004

– (*continued*)

Age	National	North	Centre	Lisbon	Alentejo	Algarve
52	€16,709	€15,202	€13,291	€20,965	€14,281	€15,595
53	€16,165	€15,006	€13,067	€21,020	€14,068	€14,931
54	€17,526	€15,250	€13,158	€21,075	€13,612	€14,653
55	€16,504	€15,379	€13,459	€20,312	€13,731	€15,434
56	€15,437	€15,251	€13,343	€21,297	€14,298	€15,507
57	€15,557	€15,313	€12,612	€20,181	€14,629	€15,402
58	€15,359	€15,205	€13,018	€19,968	€13,632	€14,444
59	€16,881	€16,023	€14,525	€19,495	€13,140	€15,262
60	€15,727	€15,726	€13,192	€19,362	€13,180	€15,151
61	€16,103	€15,792	€12,819	€19,901	€13,359	€13,546
62	€15,954	€15,860	€13,088	€20,745	€13,340	€14,257
63	€15,629	€15,452	€13,850	€18,797	€13,298	€16,413
64	€15,460	€15,489	€13,070	€17,956	€13,426	€14,059
Average (50–64)	€16,079	€15,356	€13,288	€20,160	€13,703	€15,050
National	**€20,255**					

Note: National values are weighted averages according with each age, sex and region population size.

Appendix 2

		Hospitalizations	Medical appointments (all)	Medical appointments (all hospital specialties§)	Medical appointments (general practitioners)	Medical appointments (rheumatology)	Home care assistance
Self- reported RD	Early retirement	a) 18.0%; b) 2.5%	c) 95.7%; d) 7.8 (6.4–9.2)	c) 74.9%; d) 5.3 (3.7–6.8)	c) 89.8%; d) 3.9 (3.3–4.6)	c) 8.8%; d) 2.7 (1.9–3.4)	c) 2.5%
	No early retirement	a) 10.0% ($P = 0.10$)*; b) 2.5% ($P = 0.99$)	c) 87.1% ($P = 0.06$)*; d) 6.9 (5.9–7.9)	c) 55.2% ($P = 0.0007$); d) 5.2 (4.3–6.0)	c) 78.1% ($P = 0.02$)*; d) 4.0 (3.4–4.7)	c) 10.8% ($P = 0.42$)*; d) 2.4 (1.9–2.9)	c) 1.0% ($P = 0.06$)
	All self-reported RD	a) 12.8%; b) 2.5%	c) 90.1%; d) 7.2 (6.4–8.1)	c) 62.1%; d) 5.2 (4.4–6.0)	c) 82.2%; d) 4.0 (3.5–4.5)	c) 10.1%; d) 2.5 (2.1–2.9)	c) 1.5%
Non-RD (unknown RD)§	Early retirement	a) 11.9%; b) 0.3%	c) 91.3%; d) 5.5 (4.4–6.6)	c) 56.5%; d) 4.1 (2.9–5.4)	c) 83.5%; d) 3.2 (2.8–3.6)	c) 2.8%; d) 2.1 (1.3–2.9)	c) 0.7%
	No early retirement	a) 7.6% ($P = 0.21$)*; b) 0.6% ($P = 0.32$)	c) 82.4 ($P = 0.0002$)*; d) 4.2 (3.9–4.6)	c) 49.4% ($P = 0.12$); d) 3.2 (2.8–3.5)	c) 70.3 ($P < 0.0001$)*; d) 2.7 (2.5–3.0)	c) 1.1% ($P = 0.06$)*; d) 1.4 (1.2–1.7)	c) 1.3% ($P = 0.33$)
	All non-RD§	a) 8.8% ($P = 0.11$)**; b) 0.5% ($P < 0.0001$)**	c) 84.8% ($P = 0.25$); d) 4.6 (4.2–5.0)	c) 51.4% ($P = 0.008$); d) 3.4 (3.0–3.9)	c) 73.9% ($P = 0.05$); d) 2.9 (2.7–3.1)	c) 1.6% ($P < 0.0001$); d) 1.7 (1.3–2.2)	c) 1.2% ($P = 0.46$)
All		a) 10.1%; b) 1.2%	c) 86.6%; d) 5.5 (5.2–5.9)	c) 55,0%; d) 2.3 (2.0–2.5)	c) 76.8%; d) 3.3 (3.1–3.5)	c) 4.5%; d) 2.3 (2.0–2.7)	c) 1.3%

RD, rheumatic diseases.
a) Proportion of hospitalized patients in the previous 12 months/ b) proportion of hospitalized patients in the previous 12 months directly caused by RD. c) Proportion of users in the previous 12 months/ d) mean number of consumption per user.
§All participants who did not self-reported RD were classified has non-RD. *P-values: early retirement vs no early retirement. **P-values: RD vs non-RD. §All medical appointments except general practitioners.

Please cite this article in press as: Laires PA, et al., The economic impact of early retirement attributed to rheumatic diseases: results from a nationwide population-based epidemiologic study, Public Health (2016), http://dx.doi.org/10.1016/j.puhe.2016.07.004

Appendix 3. Logistic regression results.

	Outcome: general early retirement		Outcome: early retirement due to RD	
	Univariable OR (95% CI)	Multivariable OR (95% CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Rheumatic diseases (self-reported)	1.5 (1.1–2.0)	1.4 (1.0–1.8)	11.9 (5.8–24.4)	6.8 (3.7–12.4)
Age	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Gender (female)	0.7 (0.5–0.9)	0.5 (0.4–0.7)	4.1 (2.0–8.3)	1.9 (1.0–3.4)
Area of residence				
North	1	1	1	1
Centre	1 (0.7–1.4) NS	0.9 (0.7–1.4)	1.3 (0.5–3.5) NS	1.5 (0.7–3.3) NS
Lisbon	0.9 (0.6–1.4) NS	1.1 (0.7–1.7) NS	1.4 (0.3–5.4) NS	1.7 (0.6–4.9) NS
Alentejo	1.0 (0.7–1.6) NS	1.1 (0.7–1.8) NS	1.8 (0.6–5.1) NS	2.3 (0.9–5.9) NS
Algarve	0.7 (0.4–1.3) NS	0.6 (0.3–1.2) NS	0.5 (0.1–2.7) NS	0.9 (0.2–4.9) NS
Azores	0.9 (0.6–1.4) NS	0.9 (0.6–1.6) NS	2.4 (0.9–6.5) NS	2.9 (1.2–6.9)
Madeira	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.7 (0.2–2.0) NS	0.6 (0.2–1.7) NS
Educational level				
Low	1	–	1	1
Medium	0.7 (0.5–1.1) NS	–	0.3 (0.1–0.7)	0.5 (0.3–1.1) NS
High	0.6 (0.4–0.8)	–	0.2 (0.1–0.4)	0.3 (0.1–0.8)
Chronic diseases (self-reported)				
Cardiovascular§	1.8 (1.3–2.4)	–	2.2 (1.1–4.3)	–
Diabetes	1.9 (1.4–2.8)	–	2.3 (0.8–6.9) NS	–
Pulmonary	1.8 (1.0–3.1)	–	1.2 (0.5–2.9) NS	–
Allergy	1.1 (0.6–1.5) NS	–	2.6 (1.0–6.5)	–
Gastrointestinal	1.7 (1.2–2.5)	1.7 (1.2–2.4)	1.5 (0.8–2.9) NS	–
Neoplasic	1.5 (0.9–2.4) NS	–	0.7 (0.2–2.2) NS	–
Mental	1.6 (1.1–2.3)	–	4.4 (1.9–10.3)	2.4 (1.3–4.5)
Neurologic	2.8 (1.7–4.4)	2.9 (1.6–5.2)	1.3 (0.5–3.5) NS	–

OR odds ratio, CI confidence interval*.
All initial multivariable models were adjusted for age, gender, area of residence (NUTSII), education level (primary school or less, medium and high), household income and other chronic diseases. Cofactors were excluded in the stepwise method if $P > 0.05$. Cofactor age was transformed (mean centring) due to high multicollinearity (variance inflation factor >10). Other covariates of potential interest (e.g. smoking status, physical exercise and marital status) were also tested, but no significant association was found.
§Cardiovascular includes risk factors hypertension and hypercholesterolaemia.

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Article D: Early Exit From Work Attributable to Osteoarthritis and its Economic Burden

Pedro A. Laires, Helena Canhão, Ana Rodrigues, Mónica Eusébio, Miguel Gouveia, Jaime C. Branco

Ago 2016 (submitted)

EARLY EXIT FROM WORK ATTRIBUTABLE TO OSTEOARTHRITIS AND ITS ECONOMIC BURDEN

ABSTRACT

OBJECTIVES: To describe the association of clinically confirmed osteoarthritis (OA), including its most frequent location (i.e. knee), with early exit from work and to calculate its economic burden (productivity loss).

METHODS: We analysed data from the population-based EpiReumaPt study (Sep2011-Dec2013). 10,661 inhabitants were surveyed to capture all cases of rheumatic and musculoskeletal diseases within a representative sample of the population. We analysed all participants aged 50-64 years, near the official retirement age and all OA cases were clinically validated, according to the ACR classification criteria. For retired participants, years of working life lost (YWLL) were determined as the difference between each OA participant's age and the respective retirement age when self-reported retirement was caused by a rheumatic condition, while the potential YWLL (PYWLL) was the difference between official and actual retirement ages. An official wage database was used to estimate productivity by gender, age and region using the human capital approach. The effects of OA on the likelihood of early exit from paid employment and the attributable fractions estimates were obtained at the individual level by multivariable logistic regression.

RESULTS: In the survey, more than half of the population aged between 50 and 64 years were out of paid work (51.8%) and had an OA prevalence of about 30% (29.7%; men: 16.2% and women: 43.5%. Knee OA: 18.6%; hand: 12.6%; hip: 3.6%). OA is associated with early exit from paid employment, specifically knee OA (OR: 2.25; CI: 1.42-3.59; p=0.001). Other OA locations do not have a statistically significant effect on work loss. Early exit from paid employment due to OA led to a total of 143,262 YWLL and 338,822 PYWLL (84 and 198, respectively, per 1000 inhabitants in the age group 50-64). The estimated annual indirect cost attributable to OA was €656 million (€384 per capita; €1294 per OA patient and €2095 per OA patient out of work). Females contributed with 61.6% of these costs (€404 million).

CONCLUSIONS: A considerable amount of working life loss and indirect costs are associated with OA. Premature withdrawal from employment attributable to OA amounts to approximately 0.39% of the national GDP. The high prevalence and the impact of this disabling chronic disease highlight the need to prioritize policies

targeting early exit from work in OA and research on the cost-effectiveness of interventions aiming to reduce such economic burden.

INTRODUCTION

In many western countries the population is ageing due to increasing longevity and falling birth rates.[1] However, a high rate of exit from the workforce persists as a consequence of numerous factors, including health-related problems.[2-6] Several studies show that ill-health is a risk factor for transitions between paid employment and various forms of non-employment, including retirement and unemployment.[3,7,8]
Osteoarthritis (OA) is the most common joint condition in adults and globally it is the fastest increasing major health condition. It is recognized as one of the leading and rapidly growing causes of disability. Its most disabling manifestation (joint pain) is strongly associated with common forms of disability, including work restriction.
The increasing prevalence of chronic health conditions, especially OA, in people near the retirement age raises questions about the viability of attempts to extend working life. However, research about the effect of OA on work participation and its economic burden is still scarce.[12,13]

Thus, the main aim of this study is to describe the association of clinically confirmed OA, including its most frequent location (i.e. knee), with early exit from work and to calculate the respective productivity loss (i.e. indirect costs and YWLL).

METHODS

Sample

This study uses the first national, cross-sectional, population-based study on rheumatic diseases in Portugal – the EpiReumaPt study.[14] The methodology of EpiReumaPt has been detailed elsewhere.[15] Briefly, EpiReumaPt (September 2011 - December 2013) randomly selected a representative sample of 10,661 adult subjects who self-reported several data following a questionnaire applied by trained staff. Additionally, rheumatologists performed a standardized physical examination and appropriate labouratory/imaging evaluation on those participants with rheumatic complaints/symptoms.

For the purposes of this analysis we used data from all EpiReumaPt participants aged between 50 and 64 years, near the official retirement age (1,065 men and 1,727 women).

Measures

The following self-reported measures were used: major chronic diseases (yes/no: diabetes, cardiovascular diseases including risk factors such as hypertension and high cholesterol, allergy, pulmonary disease, gastrointestinal disease, neurological disease, mental disease and cancer); comorbidity score (built as the sum of all aforementioned chronic illnesses); body mass index (BMI); quality of life (using the final 0-100 score from the SF-36 Health Survey[16,17] and its eight items separately, including the bodily pain index; and the European Quality of Life questionnaire with five dimensions and three levels validated for Portugal, EQ-5D index[18,19]); longstanding musculoskeletal pain (≥3 months); pain interference with work activities (i.e. pain affecting labour and domestic activities based on the SF-36 question: "During the past 4 weeks, how much did pain interfere with your normal work, including both work outside the home and housework?"); functional capacity (0-3 score from the Health Assessment Questionnaire, HAQ[20]); marital status; and educational level (classified into 3 major levels according to the highest degree completed: primary school or less, basic education between primary and secondary levels, and secondary education or more, including university degrees).

In this analysis we considered the presence of OA through clinical confirmation initially done by a rheumatologist and then validated by a team of 3 experienced rheumatologists, according with the ACR classification criteria, of at least one type of OA: knee OA,[21] hip OA[22] and hand OA.[23] All those without any of these OA types were considered to be non-OA (non-OA may include cases with spondylarthritis). We also used OA-specific variables collected by the rheumatologists during their evaluation, such as the Knee injury and Osteoarthritis Outcome Score (KOOS)[24], a commonly used patient-reported outcomes tool for patients with knee OA, including OA pain characterization. Regarding the case definition for the main outcome, individuals were directly asked about their employment status and all those who did not report any kind of paid work (part- or full-time), including housekeepers without a regular salary, and those in official early retirement or disability pensions, were

included in the early exit from paid employment group. All those reporting any form of regularly paid work were considered employed. This definition was used elsewhere in previous research.[8,25] A broader definition of early withdrawal from work enables to take into account the existence of different pathways to early retirement. However, we also considered relevant to separately analyse more specific types of exit from work, including pure early retirement and unemployment.

Years of Working Life Lost (YWLL) and Inactivity Ratio

YWLL were determined for OA cases with premature retirement due to rheumatic disease estimated as the difference between each participant's age at the time of the survey and the respective retirement age, while the potential YWLL (PYWLL) is the difference between official and actual retirement ages. PYWLL assumes there is no return to work. We also calculated the percentage of time in inactivity (Inactivity Ratio = YWLL/Active age-range [15-64 years old]). We excluded all OA participants with concomitant inflammatory rheumatic diseases with very likely impact on retirement, such as rheumatoid arthritis and spondylarthritis. All cases with known retirement data were also excluded if prior to onset of OA symptoms.

Indirect Costs

In order to calculate indirect costs of premature work loss associated with OA in Portugal´s mainland we adopted society's perspective and used the human capital approach. This method estimates productivity by valuing healthy time lost due to OA using market wage rates, which can be viewed as the loss of an investment in a person's human capital. Early exit from paid employment associated with OA was assessed through logistic regression models. A good measure of the impact of OA in the early exit from paid employment may be the population attributable fractions (PAF), which take into account both the strength of the association between OA and early exit from work, as measured in the logistic models, and the prevalence of OA in the surveyed population. PAF were calculated as the resulting proportional change in the probability of premature work withdrawal following a counterfactual exercise where the presence of OA is artificially eliminated from the sample. This recalculated probability of exit from work was then used to estimate the indirect costs attributable to OA by multiplying each observation's probability change with the corresponding

unit value of production. The unit values of production were assessed by obtaining the market wage rates from national public sources for 2013.[26] These figures needed to be grossed up by social security contributions. This approach yielded an annual average value of €24,891 for men and €16,079 for women, for ages between 50 and 64 years. All unit values of production were stratified by age, gender and geographic region (Appendix 1).

Statistical Analysis

Descriptive analysis was mainly performed comparing early withdrawals from work (including early retirees) versus the employed participants of the analysed sample. Prevalence of early exit from work and other characteristics were computed as weighted data, in order to take into account the stratified sampling design of the survey. Missing values were not replaced and all statistics were calculated based on non-missing values. To explore the association between OA and early exit from work we built multivariable logistic regression models by means of a manual stepwise technique (backward elimination) using the following potential confounders: age, gender, region, marital status, education, household income, BMI and chronic diseases. Pain and disability were not included in the multivariable models since they are considered intermediate factors of OA within the studied etiologic model, as further explained bellow.[27,28] Their association with the outcome was instead analysed separately adjusted for age, gender and region. All statistical analyses were carried out using Stata IC V.12 (StataCorp, 2011. Stata Statistical Software: Release 12. College Station, Texas, USA: StataCorp LP).

RESULTS

In the survey, more than half of the population aged between 50 and 64 years were out of paid work (51.8%. Table 1) and had an OA prevalence of about 30% (29.7%; men: 16.2% and women: 43.5%. Knee OA: 18.6%; hand: 12.6%; hip: 3.6%). Lower education and monthly household income were more frequent in the premature withdrawals, while the marital status single was more likely found in the people employed. The out of work group had a worse health status, with higher comorbidity scores, lower quality of life and lower functional capacity. Higher prevalence of diabetes and neurologic disorders were also found in this group. Particularly, in

comparison to the paid employment group, OA prevalence was significantly higher in all other groups (Table 1).

Table 1 - General description of the sample by employment status: EpiReumaPt ages 50–65

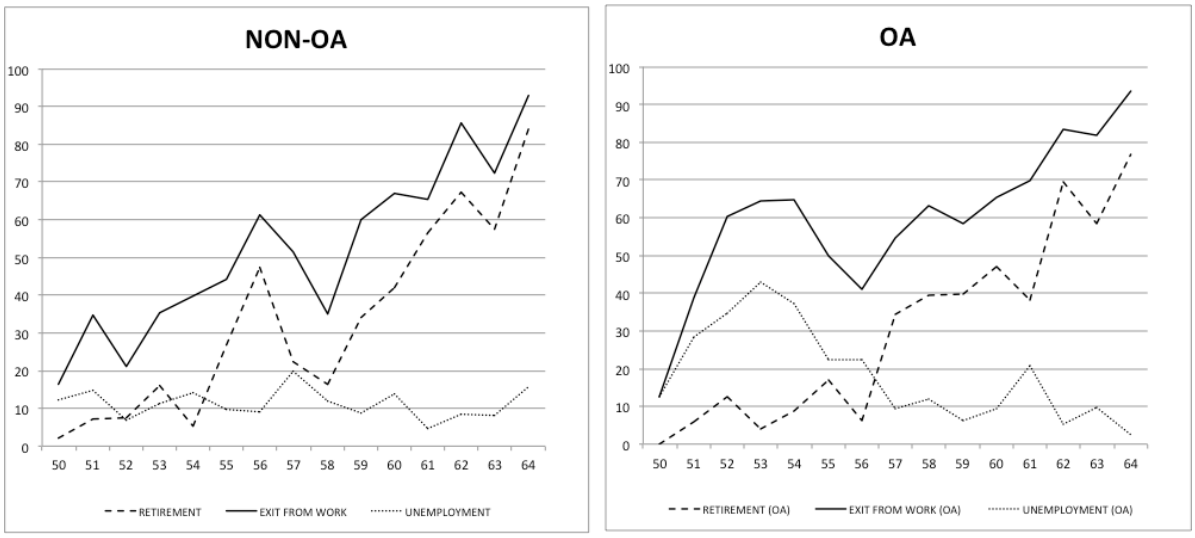
	UNEMPLOYMENT	EARLY RETIREMENT	EXIT FROM WORK	PAID EMPLOYMENT
Employment Status	12.2%	30.2%	51,8%	48.2%
Age (years)	55.2 (p=0.192)*	59.9 (p<0.001)*	58.2 (p<0.001)*	54.6
Gender (female)	55.3% (p=0.187)	44.2% (p=0.757)	52.2% (p=0.305)	46.3%
Educational Level				
Primary or less	55.0%	64.0%	63.4%	37.3%
Medium	23.3%	17.6%	19.6%	28.5%
High	21.7% (p=0.024)	18.4% (p<0.001)	17.0% (p<0.001)	34.2%
Marital Status				
Single	11.7%	3.4%	5.7%	14.9%
Married / Consensual union	70.6%	77.3%	76.2%	64.5%
Divorced	14.3%	10.4%	10.3%	15.3%
Widowed	3.4% (p=0.673)	8,9% (p=0.002)	7.8%(p=0.007)	5.2%
Body Mass Index				
Underweight (<18.5m^2/kg)	0%	0.5%	0.5%	0.4%
Normal (18.5-25m^2/kg)	28.5%	25.7%	27.0%	30.5%
Overweight (25-30m^2/kg)	44.6%	50.3%	46.3%	46.7%
Obese (≥30m^2/kg)	27.7% (p=0.788)	23.5% (p=0.801)	26.2% (p=0.762)	22.4%
Clinically Confirmed OA	42.8% (p<0.001)	32.1% (p=0.08)	35.4% (p=0.003)	23.5%
Knee OA	29.0% (p<0.001)	22.0% (p=0.005)	24.2% (p<0.001)	12.6%
Hand OA	14.3% (p=0.413)	12.3% (p=0.797)	13.6% (p=0.405)	11.6%
Hip OA	3.1% (p=0.795)	4.2% (p=0.809)	3.6% (p=0.998)	3.6%
Chronic Diseases (self-reported)				
Cardiovascular	60.6% (p=0.740)	62.8% (p=0.991)	63.7% (p=0.874)	62.8%
Diabetes	10.1% (p=0.180)	17.5% (p=0.003)	15.9% (p<0.001)	6.4%
Pulmonary	11.5% (p=0.147)	7.5% (p=0.407)	9.9% (p=0.110)	5.0%
Allergy	22.4% (p=0.411)	20.5% (p=0.242)	22.4% (p=0.356)	27.5%
Gastrointestinal	22.6% (p=0.460)	26.6% (p=0.114)	25.5% (p=0.102)	19.1%
Neoplasic	5.9% (p=0.458)	6.5% (p=0.282)	5.7% (p=0.338)	3.9%
Mental	15.8% (p=0.493)	13.6% (p=0.942)	17.2% (p=0.130)	13.4%
Neurologic	1.6% (p=0.644)	6.7% (p=0.005)	4.8% (p=0.004)	1.2%
Comorbidity Score	1,87 (p=0.471)	2.03 (p=0.10)	2.04 (p=0.03)	1.74
Longstanding Musculoskeletal Pain	47.0% (p=0.049)	39.7% (p=0.399)	43.9% (p=0.073)	34.8%
Functional Capacity - HAQ	0.48 (p=0.012)	0.43 (p=0.033)	0.47 (p=0.002)	0.28
Quality of Life – EQ-5D	0.72 (p<0.001)	0.79 (p=0.152)	0.75 (p=0.002)	0.83

** all p values versus paid employment. OA, Osteoarthritis; HAQ, Health Assessment Questionnaire; EQ-5D, European Quality of Life index.*

The participants with OA had more comorbidities (Comorbidity score: 2.3 vs 1.7; p<0.001), in particular diabetes, gastrointestinal and mental disorders, and were more likely to self-report other main chronic diseases (age, sex and region adjusted OR: 1.70; CI: 1.07-2.69; p=0.023). OA participants had worse quality of life

measured by all SF-36 items (Appendix 2), especially the bodily pain index (54.9 vs. 72.6, p<0.001), and by the EQ-5D score (0.68 vs. 0.83; p<0.001). OA patients reported more frequently longstanding musculoskeletal pain than non-OA (52.5% vs. 34.1%; p<0.001). The OA population also score worse in functional capacity measured by the HAQ scale (0.64 vs. 0.28; p<0.001). Within the OA group, 61.8% were not working versus 47.6% for those without OA (p=0.004). Most were females (71.0% versus 41.9% for those non-OA in the out of work group; p<0.001). A non-significant difference was observed when analysing specifically early retirement (32.6% vs. 29.1%, respectively; p=0.437). Unemployment is a major early route of work loss in the OA population (17.7% vs. 9.9% for non-OA; p=0.002). The vast majority of registered unemployment lasted more than 12 months (95.8%).

Figure 1 – Prevalence of Early Exit from Work, Early Retirement and Unemployment according to ages 50-64



OA, Osteoarthritis

Figure 1 shows how unemployment rates were high among the youngest of the OA population (i.e. 50-56) whilst being surpassed by official early retirement after approximately the age of 56. A distinct dynamic is observed in the non-OA population where unemployment rates are in line with early retirement bellow age 55.

Table 2 - Logistic regression analysis by type of early exit from paid employment.

	Unemployment		Early Retirement		Early Exit From Paid Employment	
	Univariable OR (95% CI)	*Multivariable OR (95% CI)[a]*	*Univariable OR (95% CI)*	*Multivariable OR (95% CI)[a]*	*Univariable OR (95% CI)*	*Multivariable OR (95% CI)[a]*
Knee Osteoarthritis	1.97* (1.25-3.10)	2.68* (1.58-4.53)	1.37 (0.90-2.08)	-	2.22* (1.49-3.29)	2.25* (1.42-3.59)
Age	0.99* (0.97-1.00)	0.98* (0.97-1.00)	1.03* (1.01-1.04)	1.03* (1.01-1.04)	1.01 (1.00-1.03)	1.01* (1.00-1.03)
Gender (Female)	1.31 (0.83-2.09)	1.06 (0.61-1.84)	0.75 (0.47-1.18)	0.64 (0.41-1.00)	1.27 (0.80-2.00)	1.23 (0.79-1.93)
Educational level (Ref: Primary or less)						
Medium	0.89 (0.51-1.56)	-	0.47* (0.26-0.84)	0.46* (0.23-0.92)	0.41* (0.22-0.74)	0.31* (0.18-0.55)
High	0.77 (0.44-1.34)	-	0.46* (0.26-0.80)	0.62 (0.36-1.06)	0.29* (0.17-0.49)	0.49* (0.27-0.89)
Marital Status (Ref: Single)						
Married / Consensual union	0.85 (0.36-1.99)	-	4.38* (1.81-10.57)	4.21* (1.62-10.92)	3.11* (1.30-7.43)	5.28* (2.24-12.45)
Divorced	0.97 (0.36-2.57)	-	2.89 (0.97-8.63)	2.99 (0.97-9.22)	1.77 (0.64-4.87)	1.78 (0.69-4.58)
Widowed	0.41 (0.13-1.29)	-	6.14* (2.23-16.93)	6.08* (2.00-18.48)	3.93* (1.50-10.29)	4.04* (1.34-12.17)
Chronic Diseases						
Cardiovascular	0.88 (0.55-1.42)	-	0.97 (0.58-1.62)	-	1.04 (0.64-1.68)	-
Diabetes	0.87 (0.47-1.61)		2.25* (1.30-3.89)	1.92* (1.09-3.41)	2.78* (1.67-4.65)	-
Pulmonary	0.98 (0.43-2.24)	-	2.08 (0.83-5.21)	-	2.08 (0.84-5.15)	-
Allergy	0.86 (0.51-1.44)	-	0.70 (0.41-1.20)	-	0.76 (0.43-1.33)	-
Gastrointestinal	1.02 (0.63-1.66)	-	1.40 (0.89-2.23)	-	1.45 (0.91-2.31)	-
Neoplasic	1.27 (0.50-3.26)	-	1.61 (0.70-3.70)	-	1.51* (0.62-3.65)	
Mental	1.04 (0.64-1.70)	-	0.82 (0.54-1.23)	-	1.34 (0.91-1.99)	-
Neurologic	0.50 (0.15-1.59)	-	4.83* (2.19-10.66)	5.00* (1.95-12.83)	4.17* (1.83-9.50)	4.58* (1.40-15.00)
Household Income (Ref: ≤€500)						
>€500 and ≤€1000	0.31* (0.18-0.55)	0.36* (0.20-0.64)	0.84 (0.43-1.62)	-	0.43* (0.23-0.80)	0.40* (0.23-0.69)
>€1000 and ≤€2000	0.10* (0.04-0.24)	0.12* (0.05-0.28)	0.98 (0.45-2.12)	-	0.26* (0.12-0.54)	0.25* (0.12-0.53)
>€2000	0.15* (0.06-0.43)	0.18* (0.06-0.50)	0.79 (0.34-1.81)	-	0.22* (0.10-0.49)	0.25* (0.10-0.65)
Regional Controls		YES		YES		YES

*OR odds ratio, CI confidence interval, *p<0.05.*

a - All multivariable models were adjusted for age, gender, geographic region (7 main regions: North, Center, Lisbon region, Alentejo, Algarve, Azores and Madeira), marital status, education level, household income, body mass index and chronic diseases. Cofactors were excluded in the stepwise method if p>0.05 (except for age and gender).

Association between OA and Early Exit from Work

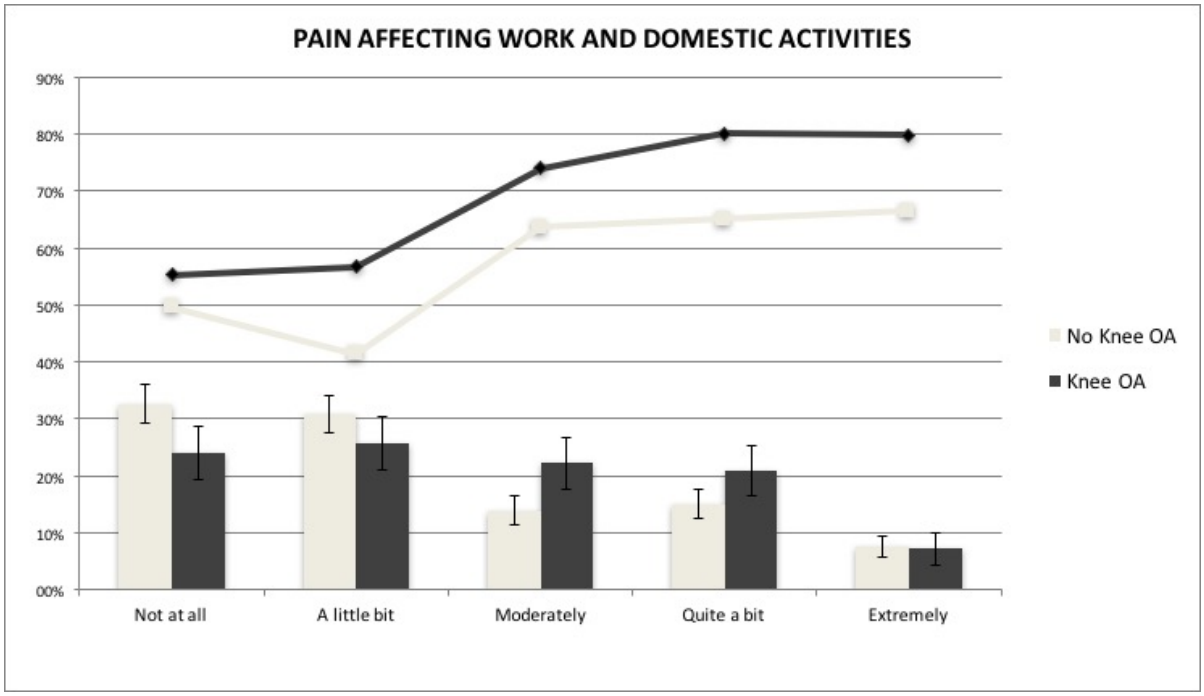
OA is associated with early exit from paid employment (OR: 1.85; CI: 1.27-2.69; *p*=0.001), but not with official early retirement (OR: 1.43; CI: 0.96-2.12; *p*=0.08). Knee location of OA is particularly associated with early exit from work (OR: 2.25; CI:

1.42-3.59; *p*=0.001. Table 2), while no significant association was observed for hand OA (OR: 1.17; CI: 0.76-1.80; *p*=0.477) or hip OA (OR: 1.04; CI: 0.36-2.99; *p*=0.938). As mentioned before, unemployment seems to be a major channel of exit from work for patients with OA (OR: 1.97; CI: 1.27-3.06; *p*=0.002), in particular for knee OA (OR: 2.68; CI: 1.58-4.53; *p*<0.001. Table 2), and for the youngest (50-57) from the sample (OR: 3.47; CI: 1.88-6.41; *p*<0.001).

Pain and Disability

Pain plays a key role in the risk of workforce withdrawal. A strong association was seen between pain interference and premature work loss, especially within the knee OA population (OR: 1.52; CI: 1.16-1.99; *p*=0.002). Those who scored worse in pain interference were more frequently out of work (Figure 2). In fact, not only the OA population was more likely to score worse (*p*=0.02) in this parameter, but also the aforementioned association between knee OA and exit from work becomes non-significant if only the subset of population with low pain interference is analysed (i.e. none to moderate pain interference. OR: 1.55; CI: 0.97-2.48).

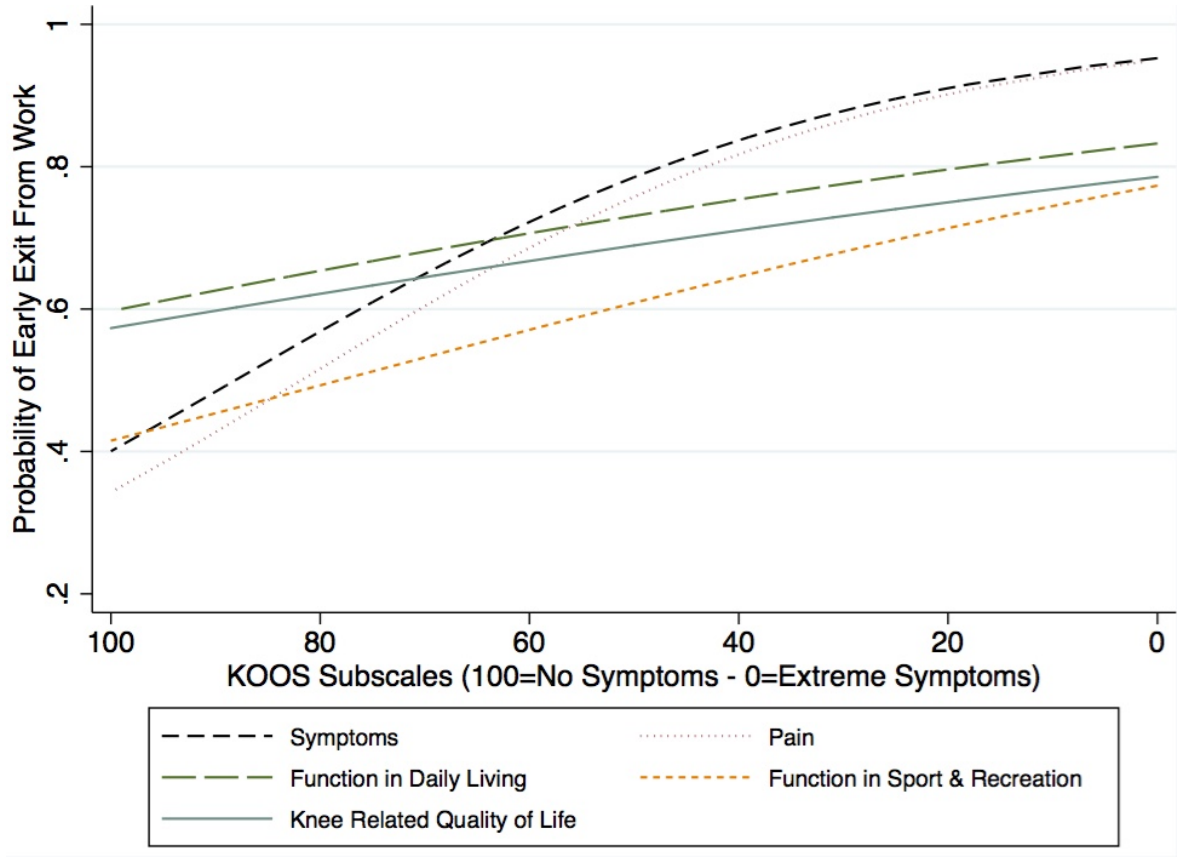
Figure 2 – Pain Affecting Work and Domestic Activities & Early Exit from Work



Lines indicate Early Exit from Work (all p-values of Knee OA versus No Knee OA groups are non-significant)
Bars indicate Pain Interference distribution by intensity levels (p=0.02) with corresponding 95% confidence intervals (vertical lines). OA, Osteoarthritis

Furthermore, looking specifically at the knee location, more impactful forms of OA are strongly related with premature work loss. Using the KOOS subscale scores it was possible to observe that knee OA with worst scores on OA symptoms, pain, quality of life, ability to perform activities of daily living and function in sport and recreation increased the likelihood of individuals being out of work. This particularly applies for pain and OA symptoms (Figure 3).

Figure 3 – Probability of early exit from work according with KOOS subscales Levels



KOOS, Knee injury and Osteoarthritis Outcome Score

In addition, knee OA patients with highest levels of disability, measured by HAQ (scores ≥ 2) are at the greatest risk of early exit from work (80.7% vs. 67.4% for all knee OA population and 51.2% for those with HAQ scores ≥ 2 but without knee OA). We estimated an almost linear relationship between levels of disability and the probability of early exit from paid employment, with its y-intercept increasing with the presence of knee OA (Appendix 3). Similar to what was observed with pain, the association between knee OA and exit from work becomes non-significant if only the

subset of population with less disability is analysed (i.e. HAQ scores below the average of the population [0.38]. OR: 0.74; CI: 0.28-1.99; *p*=0.552).

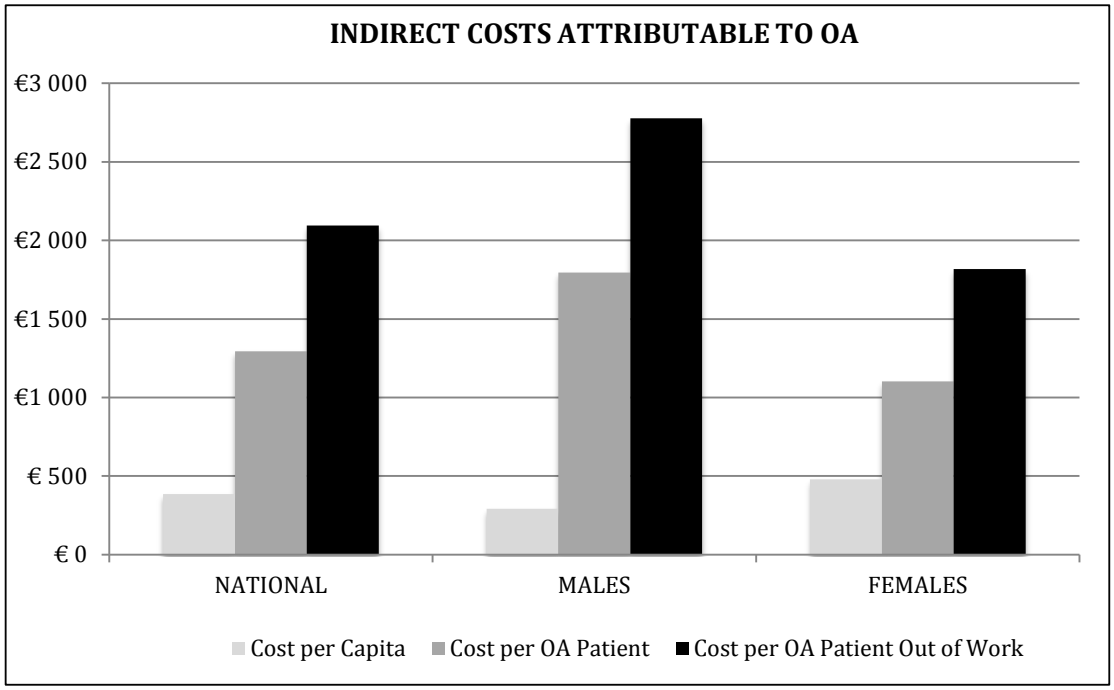
Years of Working Life Lost

Given the lack of a significant association of hip and hand OA with employment status, only knee OA cases were used to measure the productivity loss (i.e. YWLL and indirect costs). Thus, we estimated that early exit from paid employment following OA work disability led to a total of 143,262 YWLL (84 per 1000 inhabitants). Women accounted for 75.3% of these YWLL. The retirement route contributed the most for these YWLL (52.3%; 74,957 YWLL), followed by unemployment (39.9%; 57,210 YWLL) and being on disability pensions (7.7%; 11,095 YWLL). Additionally, a total of 130,602 PYWLL were estimated if early retirement is considered and 338,822 PYWLL (198 per 1000 inhabitants) for all forms of exit from work. The mean YWLL and PYWLL inactivity ratios were 10.0% and 23.7%, respectively.

Indirect Costs

The estimated annual indirect cost due to premature exit from work attributable to OA was €656 million (€384 per capita; €1294 per OA patient and €2095 per OA patient out of work). Females contributed with 61.6% of these costs (€404 million), but mean *per capita* indirect costs were larger for OA males (cost per OA male patient: €1795 vs. €1102 for females; cost per OA male patient out of work: €2776 vs. €1817 for females; Figure 4).

Figure 4 – Indirect costs per capita in the 50-64 population, per OA patient and per OA patient out of work.



OA, Osteoarthritis.

DISCUSSION

In this study using the first large-scale epidemiological population-based survey that evaluated rheumatic and musculoskeletal diseases in Portugal, we found an association between clinically confirmed OA and early exit from paid employment. However, this relationship was only found for the knee OA (not for hip and hand). We estimated that OA might have led to annual indirect costs amounting to approximately 0.39% of the national GDP (2013). Females contributed with 61.6% of this productivity loss. Males have higher mean OA indirect costs given the higher average wages.

As expected, OA patients are mostly females and older when compared with the non-OA population. They have lower levels of education, lower household income, significantly self-reported poorer quality of life and a higher number of comorbidities. These characteristics may themselves influence labour force participation. In fact, in this study we observed an association between premature work loss and lower levels of education, marital status (married or widowed), neurologic diseases and lower household income. Nevertheless, the association we found between clinically

confirmed OA and premature work withdrawal is robust and independent from other influencing factors, which is consistent with previous published data.[20-31]

OA generates disabling pain pushing the individuals to leave work prematurely. We captured pain through several alternative measures (i.e. pain interference and bodily pain item from the SF-36 questionnaire, KOOS pain subscale, and self-reported longstanding musculoskeletal pain) and, as expected, OA patients consistently reported more pain than others without the condition. In addition, we observed a straightforward relationship between pain and withdrawal from employment. This is consistent with the literature.[29,32,33] We also detected that OA patients with higher levels of disability, measured by high scores of HAQ, were at the highest risk of early exit from paid work. This also aligns with previous research[34,35] and with the etiological model behind this research, which assumes that OA generates the pain, impairment and disability that ultimately may lead to work withdrawal. Thus, we confirmed in our research that pain and disability are key factors for job loss driven by OA.

Interestingly, we did not find a statistical association between OA and official early retirement (regardless of anatomic location). OA seems instead to drive the labour force out of paid employment mainly through unemployment. This is particularly evident in the earlier ages. Afterwards unemployment is overtaken by early retirement when patients with OA get closer to the official retirement age. We did not find the same interplay between age-specific frequencies of retirement and unemployment in the non-OA population. Thus, unemployment appears to be the predominant first step to irreversible out-of-work state in OA patients, although likely not being fully converted into official retirement (in Portugal, under some circumstances, unemployment benefit may be converted into the old-age pension), since no significant association was seen with this musculoskeletal disorder. It would be relevant to further explore if this occurs because labour market policies are restricting early retirement in this sort of patients (e.g. formal rejection of early retirement applications to Social Security from employees with OA) or if other reasons are taking the lead instead. This finding highlights the need to target research and integration-oriented policies towards unemployment generated by OA. More knowledge in this area may produce employment gains since premature retirement restriction policies by themselves are insufficient to mitigate the job losses as alternative routes may take place as seen in the OA case. Although

unemployment benefits may be time limited, from the societal perspective these pathways of early exit from work embody the same economic burden (i.e. identical productivity losses) and therefore strategies that simply push individuals from one route to another are truly not socially efficient.

In this nationwide study we estimated a significant number of YWLL due to OA and annual indirect costs of €656 million euros (€2061 per patient). Previous research in other countries has measured different indirect costs of OA per patient per annum.[36-43] Comparing results of cost-of-illness studies is hampered by discrepancies across study designs, case definition, methodological choices, wage levels and source of data used.[44] Additionally, these cost results vary with time and geography. However, there are some common take-home messages: First, the economic burden of OA is considerable and closely related to its high prevalence. Second, indirect costs are likely to surpass other per patient costs (e.g. drug and other medical costs).[45-47] Third, these costs are also likely to exceed those from other chronic disabling conditions. For example, Schofield *et al*. measured annual losses of arthritis through early retirement (approximately 0.7% of GDP)[48] superior to other pathologies, such as cardiovascular disease,[49] diabetes[50] and mental conditions.[51]

We estimated an even higher number of potential years of working life still to be lost if no return to work happens until the official retirement age in the OA population. In fact, on average the estimated PYWLL cut by almost a quarter the whole potential working life span (i.e. 23.7% of inactivity ratio). This finding highlights the need to promote return to work policies, in particularly for the youngest unemployed. Since OA is degenerative return to work may became progressively more difficult as the disease advances. However, there are options available to reduce pain and functional disability (e.g. anti-inflammatory drugs and knee arthroplasty), which allied to vocational rehabilitation might allow some OA patients to return to work.[52] Cost-effectiveness evaluations of this sort of interventions should take into account such economic offsets. For instance, a recent study estimated significant societal savings from all knee arthroplasties performed in the United States.[53] On the other hand, this type of evaluations concerning non-medical vocational rehabilitation interventions are still scarce in OA.[12,13] Thus, data from this study can also be important to pave the way for cost-effectiveness analysis of such interventions aiming to reduce productivity losses caused by OA.

This study has several limitations that must be taken into account when interpreting its results. First, it may be limited by the cross-sectional design, which does not allow for an evaluation of the temporal relationship between onset of OA and time of exit from paid employment, which would help in establishing a cause–effect relationship. Lack of available national longitudinal data made this limitation impossible to overcome. Nevertheless, onset of OA is likely to start before premature exit from paid employment and reverse causality is unlikely (i.e. early exit from work as a risk factor to OA onset). Second, wages were estimated through official statistics based on gender, region and age. Necessarily, this methodology is a rough estimate of the individual unit values of production. In particular OA patients are likely associated with lower incomes. Still, given the information available, it is the best feasible method. Third, due to the cross-sectional design, our results are right-censored, leading to likely underestimation of the results (i.e. further exit from work is more probable to occur than return to work within the sample until all participants reach the official retirement age). Finally, given the richness of the EpiReumaPt dataset we do not consider our analysis to be overly influenced by hidden confounding, since we used a considerable number of control variables that according to the literature could influence exit from work.

This study has several strengths too. It is based on a large population-based study about rheumatic diseases in Portugal. It uses confirmed diagnosis of OA done by rheumatologists. To our knowledge, this must be among the few studies focusing on indirect costs of OA based on such a representative sample specifically dedicated to rheumatic and musculoskeletal conditions, a sample that is likely to accurately reflect this particular type of economic impact on society (high external validity). It will certainly facilitate future research on the effectiveness and cost-effectiveness of interventions targeting reduced work ability due to OA. Unquestionably, this issue deserves further attention. Recently, access to early retirement was restricted in some European countries that are still lacking integration policies such as vocational rehabilitation programs. Since OA is highly disabling and prevalent, particularly at ages near the statutory retirement age, it might well be an ideal area for public policies to steer a better balance between restricting early retirement and integration policies. Moreover, OA is a musculoskeletal disease where the etiological model (from the onset of symptoms/pain to the work disability/withdrawal) may be further understood and subsequently disrupted by effective health interventions.

In conclusion, this population-based study unveils the impact of the association between OA, in particular the knee location, and early exit from paid employment. It describes in detail the high economic burden underlying such association. The findings justify giving more attention to OA when discussing policies facing the ageing of developed countries. The depreciation in the stock of human capital due to OA is already extensive and given the demographic and epidemiological trends it may get even worse if nothing is done. This research should provide relevant evidence for decision makers to prioritize investments in health and policies targeting patients with OA.

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APPENDICES

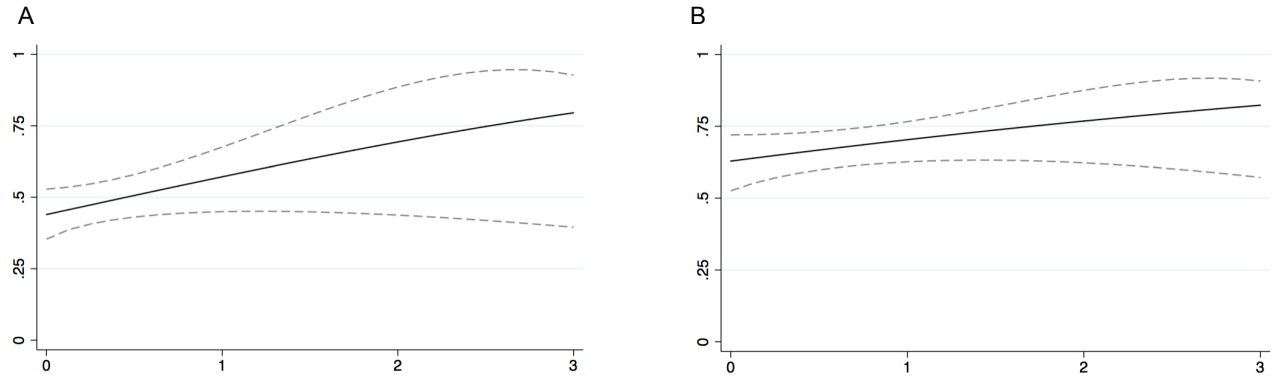
Appendix 1 is the same as Appendix 1 from Article C.

Appendix 2 - Quality of Life Results (SF-36 and EQ-5D)

	ALL OA	Knee OA	NON-OA
SF-36 physical function *(0-100 from worst to best)*	65.2	59.7	80.8 (p<0.001)*
SF-36 role limitations because of physical health problems	59.8	57.7	77.3 (p<0.001)
SF-36 bodily pain	54.9	51.2	72.6 (p<0.001)
SF-36 social functioning	80.3	78.7	87.8 (p<0.001)
SF-36 general mental health	58.8	59.9	69.7 (p<0.001)
SF-36 role limitations because of emotional problems	71.2	67.2	85.3 (p<0.001)
SF-36 vitality	51.4	51.1	61.9 (p<0.001)
SF-36 general health perceptions	47.8	47.3	56.6 (p<0.001)
SCORE EQ-5D *(0-100 from worst to best imaginable health state)*	0.68	0.66	0.83 (p<0.001)
SCORE HAQ *(0-3 from best to worst)*	0.64	0.61	0.28 (p<0.001)

OA, Osteoarthritis; SF-36, Short-Form Health Survey; EQ-5D, European Quality of life Questionnaire.
**All p values: OA versus non-OA.*

Appendix 3 – Relationship between disability levels and probability of early exit from work (by presence of knee OA). Y-axis: Probability of early exit from work; X-axis: Disability level measured by the HAQ Score.



A: Without knee OA; B: With knee OA.
OA, osteoarthritis; HAQ, Health Assessment Questionnaire.
The confidence interval consists of the space between the two dashed lines.

PART 3 – INTERVENTIONS TO AVOID EARLY RETIREMENT ATTRIBUTABLE TO RHEUMATIC DISEASES

Article E: Interventions aimed at Preventing Early Retirement due to Rheumatic Diseases

Pedro A. Laires, Miguel Gouveia, Helena Canhão

Jun 2016 (submitted)

INTERVENTIONS AIMING TO REDUCE EARLY RETIREMENT DUE TO RHEUMATIC DISEASES

ABSTRACT

INTRODUCTION: Aging of the population and early retirement translates into productivity losses to society. Persistence of working life is crucial to counteract this sustainability issue faced by western countries. Musculoskeletal and rheumatic diseases (RD) may cause work disability and early exit from work. The objective of this article is to review the current knowledge about interventions aiming to reduce early retirement of RD patients.

METHODS: We searched PubMed and The Cochrane Library for studies either in English or Portuguese between January 2000 and June 2016 that evaluated the impact of interventions targeting early retirement in RD patients still at work. We also searched for grey literature from Portuguese institutional repositories.

RESULTS: We identified several published studies testing pharmacologic and non-pharmacologic vocational rehabilitation interventions. None was specifically identified for Portugal. The general low quality of the literature and its inconsistency makes it unfeasible to draw definitive conclusions. However, some broad recommendations might be outlined. An effective intervention must: 1) act upon different levels (e.g. RD patient, workplace), involving several stakeholders (e.g. rheumatologists, occupational physicians, employers); 2) prioritize the right patients (e.g. more disabling RD); and 3) consider the patients' role, for instance by including an element of patient education and support. Despite the lack of good quality evidence on this field, there seems to be a growing interest in the international scientific community with several ongoing studies promoting such interventions. This promising data will be very useful to set up effective policies.

CONCLUSIONS: This article summarizes the current knowledge about the impact of interventions to avoid or mitigate early retirement in RD patients. It highlights the demand for further research and it also contributes to aware decision-makers about the relevance of this topic, particularly in Portugal.

INTRODUCTION

The world has continued to observe an increase in the life expectancy.[1] The old-age dependency ratio is rising steadily in most western countries, which are currently facing a growing economically dependent elderly population.[2] In Portugal, for instance, in 1980 there were a total of 1.8 million pensions with a ratio of 4 active age people per each Social Security old-age pensioner, but now there are over 3.6 millions pensions (including both the Social Security System and the Public Administration Retirement Fund) and a ratio of 2.6.[3] Life expectancy at 65 was 13.5 in 1980, while now it is 19.1.[4] At the same time, the median age of retirement continues to be below the official age (defined as the age at which women and men are entitled to draw a full retirement pension).[5,6]

Despite the recent overall increase in the median retirement age, it has been increasing at a much slower pace than life expectancy, which leads to sustainability problems that will force all countries to take action sooner or later. In fact, a trend with early exit from employment is hardly feasible and provides a major challenge to social and health policies. In particular, Portugal is already among the oldest countries in the world, with one of the highest old-age dependency ratios and it is at the forefront of this general problem regarding premature work withdrawal.[2]

There are different routes of entry into early retirement, including long-term unemployment, disability and pure early retirement.[7-11] These pathways lead to the same economic outcome: exit from the labour market in the later stages of working life and subsequent loss of productivity for society. Thus, temporary forms of premature work loss generally pave the way to definitive early retirement. This must be taken into account prior to the planning and implementation of possible interventions that might adjourn definitive decision of retirement.

This article reviews the available evidence regarding interventions aiming to reduce early retirement due to musculoskeletal and rheumatic diseases (RD).

METHODS

The information source used was PubMed, maintained by the US National Library of Medicine, and The Cochrane Library (including The Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of

Abstracts of Reviews of Effects, Health Technology Assessment Database). We searched for studies either in English or Portuguese between January 2000 and June 2016, combining relevant keywords, such as “retirement”, “job loss”, “job retention”, “exit from work”, “work participation”, “employment status”, “sick leave”, “work disability”, “rheumatic diseases”, “musculoskeletal diseases” and “arthritis”. We also searched for grey literature from Portuguese institutional repositories. The objectives of this search were specified by the following PICO framework: Population - RD adults still at work who experience, or are likely to experience, disability; Intervention - Any vocational rehabilitation intervention (pharmacologic and non-pharmacologic); Comparison – any or other intervention (including the standard practice); Outcomes - early exit from work, including early retirement.

DETERMINANTS OF EARLY RETIREMENT

The first step to set up effective interventions or even to start research on their effectiveness is to understand the bases of early retirement. The literature already has comprehensive evidence about determinants of early retirement and/or risk factors that might explain the retirement decision. This long list of possible variables might be clustered in 5 main domains: financial, occupational, sociodemographic, lifestyle and ill-health conditions (Table 1).[v] Obviously, the precise effect of each one of these possible determinants is different for each context. One the one hand we cannot expect that a given determinant of early retirement found to be significant in a certain country will also be found significant in another country. On the other hand determinants identified to influence a specific type of early retirement may not significantly affect other sorts of retirement. Furthermore, determinants of early retirement may interact. For instance, ill-health may have a relatively smaller impact on the hazard of retirement when policies generate strong financial incentives to retire early.[12] In contrast, policies that create generous disability pension schemes are expected to suffer more impact from ill-health on the hazard into early retirement. Thus, it is of paramount importance to frame the research into the exact setting in which one wants to intervene. Available literature may be useful to guide the overall strategy, but context-specific data is absolutely required to design effective actions aiming to put off early retirement.

[v] *Table 1 from the General Introduction section.*

Finally, it is worth noting that some qualitative studies identify other relevant factors affecting early retirement related with the individual's perception and experience towards the environment, such as conflicts at work, the wish to do other things outside of work, enjoy life, have more flexibility, spend more time with a spouse or grandchildren, and care for others.[13] This brings an additional layer of complexity to this social problem that ideally should not be forgotten when defining effective interventions.

ILL-HEALTH AND RHEUMATIC DISEASES' IMPACT

Although the effect of health status on early retirement has long been recognized, that effect is not always straightforward due to the interdependence with other types of determinants. For instance, chronic diseases, such as RD, may play a key role on early retirement because they might be prevalent and disabling, affecting daily functioning,[14,15] which is particularly relevant for occupations where working conditions cannot be modified or adjusted to a reduced work ability of employees.[16-18]. In fact, studies have already shown that the presence of certain chronic disorders is associated with a premature departure from the labour market.[19-21] However, some other studies have suggested that employees with chronic disorders tend to retire later because they likely have accumulated fewer assets during their working life, the so-called wealth effect.[22] Once again, the role and the effect of ill-health in early retirement is far from being the same across all contexts.

A lot remains to be understood about the relationship between ill-health and early retirement and the possible influence of the social context and other factors on this relationship. Moreover, since health status encompasses a broad array of underlying clinical conditions, it is also of interest to assess how specific symptoms and chronic conditions are affecting withdrawal from the workforce. Previous research has suggested associations of exit from paid employment with diseases like cancer,[23] heart disease,[24] depression,[25] disorders of the nervous system,[26,27] and others.[20,28,29]

The association with RD is particularly interesting. These diseases are highly prevalent in the western world and their clinical and functional impacts may be profound, representing major causes of disability among workers, particularly on manual-workers, who are exposed on average to harsher working conditions. Thus, workforce participation among patients with RD has received considerable attention.

Disability and productivity costs are very high, estimated at up to 4 times greater than direct RD healthcare costs.[30-34] This is of particular concern because RD, such as osteoarthritis, are projected to increase in prevalence, in part because of the ageing of the population, but also due to lifestyle factors, such as lack of physical activity and obesity.[35-37]

Some studies have analysed the RD effect on early retirement,[20,38,39,40] but unsurprisingly its isolated role is also context-dependent and influenced by the evidence source itself, reflecting differences on the type of study performed, the population under study and the explanatory variables included in the analysis.

However, regardless the context and the exact magnitude of the effect of RD on early retirement there is a theoretical underlying etiological model, which is depicted in Figure 7.[vi] RD usually generates pain and impairment, which in turn may lead to disability and ultimately to work withdrawal. In each step of this general model there are influencing factors, at least some of which may be changeable to some extent (e.g. pain control and disease activity). Thoroughly comprehension of this model is crucial to plan effective interventions to reduce RD-related early retirement.

Earlier studies were targeted to help disabled RD patients return to work (i.e. focusing the very end of the etiological model). However, in general, once people are unable to work they are unlikely to re-enter the workforce. This irreversibility is likely to be particularly true for progressing disabling conditions, such as RD. Therefore, emphasis has recently shifted towards employment loss prevention (i.e. acting on the earlier steps of the etiological model). It is better and easier to prevent premature work withdrawal than to deal with it after it occurs.[42] Our article focuses on studies that tested specific interventions following this principle. Nevertheless, it is worth noting that interventions targeting return to work may also be effective. This can be particularly true for those recently on sick leave, since there is a strong association between increased length of sickness absence and increased risk of taking a disability pension.[43] In fact, a recent review has found that some workplace interventions reduced time to (first and lasting) return to work among workers with RD on sick leave more than usual care.[44]

[vi] *Figure 7 from the General Introduction section.*

INTERVENTIONS AIMING TO REDUCE EARLY RETIREMENT

Vocational rehabilitation (also called occupational rehabilitation or work rehabilitation) is directed to employment outcomes and it can be defined as 'a process to overcome the barriers an individual faces when accessing, remaining, or returning to work following injury, illness, or impairment'.[45,46] Vocational rehabilitation may include medical and non-pharmacological management of the condition, assessment of needs, work adjustment and control measures, disability awareness training, retraining and capacity building, and support for the individual, employer, or others.[45,46] In fewer but more pragmatic words, vocational rehabilitation is whatever aids someone with a health condition to return and/or remain at work. Therefore, it encompasses all interventions that have these outcomes as their primary aim.

This is in fact the main distinction from the traditional 'treatment' intervention, which has the primary goal of treating pathology and/or relieving symptoms. This may be sufficient to enable the person to continue or return to work, but that is an indirect or secondary outcome. Vocational rehabilitation instead is directed to improving capability for work and secondarily may lead to improvement of symptoms and disease control.

Despite the fact that vocational rehabilitation should be individualized in order to meet the needs of the person it is not a matter for healthcare alone. It commonly requires a combination of healthcare and workplace assessments, to address the health problem and work issues and therefore such interventions can be targeted at a range of levels: individual (e.g. pharmacologic therapy, job coaching and training, vocational counselling; empowerment for work, self-management), environmental or organizational (e.g. work adaptations, ergonomic measures, job accommodations; interventions targeted directly at the employer).[47,48] The basic assumption is that productivity will be improved when individuals are well matched to the inherent requirements, often referred to as person-environment fit.[49] Therefore, it should require a multistakeholder approach - the individual, the employers and the healthcare professionals - working together with a common goal.

PHARMACOLOGIC INTERVENTIONS

Pharmacological interventions for RD aiming to decrease pain and inflammation may have an impact on work participation and, in the long run, in the early withdrawal from employment. This may be through their effect on disease activity, pain or physical function, which are all known predictors of work disability.[50,51] Pharmacologic interventions are disease-specific, mainly rheumatoid arthritis (RA), and can encompass drugs (e.g. anti-TNF therapy) or treatment approaches (e.g. intensive treatment regimen). Below are some of the studies that tested the impact of pharmacologic interventions on early exit from work, including early retirement:

• In 2003, Yellin E *et al*. interviewed 497 American RA patients of working age (18–64 years) about their employment status in the year of diagnosis and as of the study year. Among RA patients who had been employed at the time of diagnosis, those from the etanercept clinical trials were more likely to be employed at the time of survey. Moreover, the authors found that after adjustment for relevant factors having been in the etanercept clinical trials was associated with higher employment rates.[52]

• In 2004, Puolakka K *et al*. analysed the impact of initial aggressive drug treatment with DMARDs versus therapy with a single DMARD in the prevention of work disability in patients with early RA. 195 patients were randomly assigned to receive either combination therapy with DMARDs (sulfasalazine, methotrexate, hydroxychloroquine) plus prednisolone or single therapy with a DMARD with or without prednisolone. After 2 years, the drug treatment strategy was no longer restricted. At baseline, 162 patients (80 in the combination-treatment group and 82 in the single- treatment group) were still working or at least available for work. After 5 years of follow-up the authors found a positive impact with initial aggressive drug treatment in terms of lost productivity - including sick leave and employment loss, either temporary (unemployment) or permanent (disability pensions and retirement). However, this benefit was mainly due to the differences in sick leave. In fact, no statistically significant differences were seen in the take-up of disability pensions or early retirement.[53]

• In the same year, Kobelt G *et al*. observed a slight increase in the work capacity (from 31% to 33%, based on the proportion of patients on full time work) of 160 RA patients under 65 treated during the first year with either etanercept or infliximab in

four rheumatology units in southern Sweden. However, 2 patients retired during that period of time increasing the proportion on retirement from 14.5% to 16.2%.[54]

• In 2006, Smolen JS *et al*. verified that the proportion of patients whose status changed from employable at baseline to unemployable at week 54 was smaller in 722 RA patients receiving methotrexate plus infliximab compared with 282 RA patients receiving methotrexate alone (8% versus 14%; p=0.05).[55]

• In 2007, Wolfe F *et al*. examined the effect of anti-TNF therapy on work disability using data from the National Data Bank (NDB) for RD. They studied 3886 patients with RA who were employed at study entry, of whom 1986 received and 1900 did not receive anti-TNF therapy. After adjustment for demographics, RA severity, and comorbidity the authors did not find that anti-TNF therapy was associated with the reduction of self-reported employment loss. However, these results might be hampered by a number of limitations, including the study design (non-randomized) and the study population (<61 years old).[56]

• In 2008, Allaire S *et al*. using a nested, matched, case–control approach in a large cohort of rheumatoid arthritis patients (NDB) observed no protection of anti-TNF therapy against any or disease-attributed employment loss. However, a protective effect was found for users with shorter disease duration (<11 years. OR 0.4, 95% CI 0.2-0.9).[57]

• In the same year, Cole JC and colleagues, re-examined data from 2 clinical trials [one for RA methotrexate failure patients (n=652) and another for RA severe anti-TNF failure patients (n=391)] and found a significant reduction in the likelihood for early exit from work with abatacept treatment compared with placebo (at 6 months, 1 year and 2 years).[58]

• Also in 2008, Bejarano V *et al*. published results from a randomized controlled trial (RCT) reporting positive results on reduced employment loss for a 56-weeks period following treatment with adalimumab plus methotrexate.[59]

• Similarly, a year later, Halpern MT *et al*. have shown in an open label extension study that patients with RA who received adalimumab experienced considerably longer periods of work and continuous employment. Thus, during a 24-month period, 158 patients who received adalimumab worked 2 months longer (95% CI 1.3-2.6)

and were significantly less likely to stop working than did the 180 patients treated with DMARDs (HR 0.36, 95% CI 0.15-0.85).[60]

• In 2010, Augustsson J *et al*. using data from the Stockholm anti-TNF follow-up registry concluded that biological therapy is associated with increases in workforce participation in patients with RA.[61] Similar results have been obtained in another Swedish register for ankylosing spondylitis.[62]

• In the same year, Verstappen SM *et al*. using a large British RD registry (BSRBR, British Society for Rheumatology Biologics Register) found that compared with the use of conventional DMARDs, the use of anti-TNF did not prevent patients with RA (n=3291) from not working due to ill-health/disability (adjusted OR 0.80; 95% CI 0.36-1.81; *P*=0.596). However, RA patients in the anti-TNF group who were in remission 6 months after commencing anti-TNF therapy were less likely to exit work 3 years after inclusion in the register.[63]

• Still in 2010, van Vollenhoven RF *et al*. showed that the likelihood of gaining/ retaining employment over 2 years' treatment in early RA patients was greater for the combination therapy of abatacept plus methotrexate (n=219) than for the methotrexate alone (n=214. OR 1.53, 95% CI 1.04–2.26).[64]

• In 2013, Eriksson JK *et al*. in a randomized controlled open-label trial observed radiological superiority of biological compared with conventional combination therapy which did not translate into better work loss outcomes (i.e. monthly sick leave and disability pension days 21 months after randomization) in patients with early RA who had experienced an insufficient response to methotrexate.[65]

• More recently, in 2016, the same author and colleagues compared the long-term employment loss in methotrexate-refractory early RA patients randomized to addition of infliximab or conventional combination treatment. Of 210 working age patients, 109 were randomized to infliximab and 101 to conventional treatment. After over 7 years of follow-up in real world clinical practice, the authors observed that, compared to the year before randomization, exit from employment of these patients improved significantly, with the largest improvement during the first 3 years. However, no difference was detected between strategies, and the level of work loss days remained twice that observed in the general population.[66]

• In the same year, Olofsson T *et al*. using the Swedish Biologics Register, after 5 years of follow-up, observed a substantial decrease in work loss (i.e. mean monthly days lost and accumulated employment loss) of RA patients with high and moderate disease activity treated with anti-TNF.[67]

Many other studies explored other work-related outcomes (e.g. surrogate markers) in RD following pharmacologic interventions.[68-83]

The inconsistencies in the literature regarding the effect of pharmacologic approaches upon early retirement and overall early exit from work highlights the demand for further research and also the already mentioned need to address this topic at different levels, effectively targeting the person-environment fit.

NON-PHARMACOLOGIC INTERVENTIONS

The evidence in the currently available literature is insufficient to make definitive recommendations for policymakers, health professionals and others concerning non-pharmacologic interventions. Levels of evidence quality are relatively low and findings so far are inconsistent. It is true that this derives, at least partially, from the fact that the determinants and the factors, which affect RD-related employment loss and early retirement, differ according to the context under study. In addition, the vast heterogeneity of the interventions analysed makes it extremely difficult to set a common ground for recommendations or standard approaches ready to be applied for all environments and disease models. However, this inconsistence also finds its own roots in the quality of the studies that originated the current evidence (overall very low to moderate GRADE score).[84,85]

A recent systematic review by Oakman J *et al*.[48] was undertaken to analyse what are the most effective interventions to remain productively employed for those with persistent musculoskeletal pain, a unifying characteristic across the vast majority of rheumatic conditions. The review concluded that low numbers of participants and limited studies resulted in a low grading of the evidence and that further research is required to ensure that effective workplace interventions are developed. Previously, Palmer KT and colleagues[86] reviewed the effectiveness of interventions in community and workplace settings to reduce sickness absence and employment loss in workers with musculoskeletal disorders and also found studies typically small

(median n of 107) and limited in quality. Although they measured a significant positive median relative risk of 1.25 for the identified interventions aiming to avoid musculoskeletal-related work withdrawal, the effects were smaller in larger and better-quality studies, suggesting publication bias. Of note, this review also highlighted that no cost benefit analyses identified an intervention with statistically significant net economic benefits.[86]

A vast amount of studies focused on interventions aiming to facilitate return to work after sickness absence of employees with low back pain. However, there is already some data for other RD (e.g. chronic arthritis) and with other occupational outcomes as well, such as early retirement. Below one can find the list of the most relevant studies performed in this area (some studies also have a pharmacologic intervention):

• In 2003, Allaire SH *et al*. made a RCT with 48 months of follow-up undertaken to determine the efficacy of vocational rehabilitation, which consisted of 3 components: job accommodation, vocational counselling and guidance, and education and self-advocacy. The job accommodation component consisted of an assessment of possible health-related work place barriers to job performance (e.g. difficulty handling objects, working the required number of hours, or doing repetitive tasks) and development of solutions to the barriers that participants had identified. In the vocational counselling and guidance component, the counsellor and participant evaluated the individual's job in light of his or her RD. If problems were foreseen, possible job alternatives, requirements, and relevant resources were identified. In addition, the counsellors conveyed positive messages about each participant's ability to work. In the education and self-advocacy component, information about legal rights and responsibilities (such as the employee's responsibility to request accommodation when needed), guidance regarding disclosure issues, and skills training to increase the participant's ability to request a job accommodation in an appropriate manner were provided. The counsellors also gave the participants in the experimental group documentation about how to manage health-related employment problems and about other available resources. A total of 242 patients with RD residing in Massachusetts, USA at risk for job loss were recruited, 122 for the experimental group and 120 for the control one. Employment withdrawal was delayed in the experimental group compared with the control group. After adjustment

for potential confounders, participation in the experimental group was found to be protective against temporary or permanent work loss (OR: 0.58, 95% CI 0.34–0.99).[87]

• In 2005, Abásolo L *et al*. analysed the effect of a specific program, run by rheumatologists in Spain, in which care was delivered during regular visits and included 3 main elements: education, protocol-based clinical management, and administrative duties. Thus, the visits were structured following specific proceedings for the different diagnoses, which included education (e.g. instructions about the diagnosed RD and due self-management), pharmacologic (treatment of pain, inflammation, anxiety and depression) and non-pharmacologic treatment, and timing of diagnostic tests in a stepwise manner. 13,077 patients were included in this RCT, 7805 in the control group and 5272 in the intervention group. The program was highly efficacious in several occupational outcomes. In particular, fewer participants in the intervention group were permanently work disabled or took early retirement after 4 years.[88,89]

• In 2005, de Buck PD *et al*. conducted a RCT within the region of Leiden, the Netherlands to investigate the effectiveness of a multidisciplinary job-retention vocational rehabilitation program in RD patients at risk for job loss, consisting of a systematic assessment followed by education, vocational counselling, guidance, and medical or non-medical treatment. The program was delivered by a multidisciplinary team comprising a rheumatologist, a social worker, a physical therapist, an occupational therapist and a psychologist. An occupational physician was also connected to the team and the organization of the program was in the hands of a coordinator. The basic assessment was performed by a rheumatologist (current level of disease activity and joint destruction, presence of extra-articular manifestations or comorbidity, and extent and severity of activity limitations; prognosis regarding future impairments and activity limitations) and the coordinator (education level and previous jobs; systematic registration of the problems encountered in the current working situation, using a list of potential challenges and psychosocial situations). If necessary, additional team members were asked to see the patient to gather more information about specific aspects of the work situation. Depending on the specific problems of the individual patient, the intervention further consisted of education (such as providing written and oral information about the social security system

regarding sick leave and work disability), counselling and guidance (such as the identification of resources for adapting the work environment or work hours, promotion of work self-efficacy), or treatment (such as adaptation of the medical treatment in consultation with the referring rheumatologist, exercise therapy, occupational therapy, functional training of relevant activities, or mental restoration). All patients made at least 2 visits to the hospital in connection with the job-retention vocational rehabilitation program and the total duration of the intervention varied, and lasted 4 to 12 weeks. A total of 140 patients with a chronic rheumatic condition were randomly assigned to either this vocational rehabilitation program or usual outpatient care. In contrast with the previous studies and despite the comprehensive intervention, the authors observed no difference between the 2 groups regarding the proportion of patients having lost their employment at any time point, with 24% and 23% of the patients in the vocational rehabilitation program and outpatient care groups, respectively, having lost their work after 24 months. This could be at least partly explained by the studied population being composed by ~40% of patients already on sick leave at baseline, many of them longer than 6 weeks. Long-term sick leave usually indicates substantial limitations in work capacity and often precedes permanent work disability. Of note, this study found significant less fatigue in the intervention group, which in turn is expected to lead to more employment maintenance in the long run.[90] The authors emphasized that there was still plenty rationale for the future development and evaluation of vocational rehabilitation programs, in particular the need for early identification of RD patients at risk for work disability, namely through the broad implementation in the clinical setting of rheumatologic care of instruments to measure work disability.[91] Later, in 2007, van den Hout WB and colleagues aimed to estimate the cost-utility of this vocational rehabilitation program and concluded that its costs (€1,426 per patient, of which 20% were time and travel costs incurred by the patients) were outweighed by total savings on other health care (consultations, hospitalizations, or home nursing care) and non-health care costs (aids and appliances, productivity costs, or home help and informal care), but not significantly.[92]

• In 2011, Varekamp I *et al*. studied the effect of an employment maintenance program for employees with chronic disease (25% with RD). This group-training program consisted of six three-hour sessions every two weeks, with a seventh

session two months after the sixth. This was combined with three individual counseling sessions. It had an empowerment perspective with the aim of enhancing the knowledge, self-awareness and skills (especially communication skills) of the individuals, in order to help them solve problems at work. Participants were randomly assigned to the intervention (N=64) or control group (N=58) and after 24 months of follow-up no statistical differences were observed regarding employment maintenance, which remained high in the whole group resulting in too low power to show any significant changes. Alike de Buck PD *et al*[91] the authors observed less fatigue in the intervention group.[93]

As mentioned above, the overall quality of these studies is low, namely due to risk of bias, inconsistency and imprecision,[94] which also highlights the need for further research on this important topic. Other studies are currently ongoing to evaluate the effectiveness of specific interventions on employment retention of RD patients.[95,96]

On the other hand, some studies have already reported the effect of non-pharmacologic interventions in more temporary occupational outcomes, such as sick leave,[97] or surrogate markers of early retirement, such as assessments of function and work ability.[98-104] Some scales have been developed specifically to measure work ability in RD patients.[105]

DISCUSSION

Many studies have been conducted about interventions aiming to achieve successful outcomes in terms of RTW of workers with RD, however emphasis has shifted towards employment maintenance rather than the more likely irreversible exit from work. This article focuses on interventions to avoid early retirement while RD patients are still at work. There seems to be more consistent data on the positive effects of pharmacologic interventions than on the non-pharmacologic ones. Many reasons may explain this, namely the very nature of the interventions themselves. Non-pharmacologic job vocational activities vary immensely and its effectiveness may be difficult to replicate in different settings. Pharmacologic interventions may lower RD activity and cease pain and impairment, which in turn interfere with work disability and early retirement. It is therefore of the utmost importance that RD patients are effectively treated with the most appropriate pharmaceutical approach. Obviously, this judgment must always be done by the rheumatologist who needs to

decide on a case-by-case basis among the available treatment options. On this regard, the current trend to expand the rheumatology referral network in Portugal may bring significant productivity gains by allowing the system to effectively address the problems systematized in the etiologic model presented in this article and thereby avoiding early retirement caused by RD. Unquestionably, in order to ensure optimization of this network, effective identification and referral of RD patients at risk of job loss requires alignment with the primary care (i.e. general practitioner and occupational physicians).

Despite the overall inconsistence and low quality of information, some studies have already shown promising results for the non-pharmacologic interventions. For instance, the work done by Lydia Abásolo and colleagues[88] is being highlighted by the Fit for Work Europe initiative, which produced estimates about the effects of repeating this intervention in other European countries. Thus, extrapolating this data for all 28 Member States, the total estimated number of additional EU workers who would be available for work each day would be one million.[106] The ultimate occupational outcome from successful interventions might be so large that justifies on the one hand further research on the topic and on the other to take the risk to intervene even when uncertainty still remains about its effectiveness. The inertia on this field is already too costly and certainly the early retirement scenario is not going to improve if nothing is done otherwise. Of course, the decision should always depend on the budget required to implement a given job vocational program and due opportunity costs (i.e. the costs of the alternatives that must be forgone in order to afford a given intervention). On this regard, taking advantage of geographically or historically closed stakeholders might be a key success factor, by sharing costs and leveraging synergies and economies of scale. For instance, job vocational programs agreed upon by large employers and the nearest rheumatology department in a certain region could be a cost-effective starting point – to build the proof-of-concept of a given protocol and to pilot a broader national policy targeting early retirement in RD patients. Surely, such programs, if possible, should go along with longitudinal prospective studies in order to measure the occupational outcomes and their levels of cost-effectiveness.

In order to increase the likelihood of success of such interventions, some guidance can be drawn from the current literature. First, well-planned interventions should aim

different levels (e.g. RD patient, workplace) and should foster lean communication and alignment of all involved actors (e.g. rheumatologists, occupational physicians, employers). A coordinator could integrate all aspects of such multilevel and multidisciplinary intervention in order to better guarantee the person-environmental fit by orchestrating distinct roles and responsibilities; second, prioritizing the right patients can substantially increase the likelihood of success of a given intervention. RD patients at risk of job loss (e.g. longer duration of disease, high self-reported pain and disability measured by the health assessment questionnaire) can be prioritized leading to better and faster occupational outcomes; third, interventions should consider the patients' role and include an element of patient education, coaching and support to enable them to play an active part in the management of their condition in the workplace and also improve their self-efficacy perception.

Some steps have been taken in Portugal regarding this issue, namely the Portugal Apto.PT (Fit for Work Portugal),[107] however more political engagement should take place to ensure impactful nationwide policies and interventions targeting RD-related retirement. Hopefully, this article can also contribute to make politicians and other relevant decision-makers aware of the relevance of this topic and the possible solutions that can be, at least partially, replicated in Portugal.

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SECTION C

GENERAL DISCUSSION

In this study, we found that in Portugal self-reported RD and clinically confirmed OA are associated with early retirement and broad early exit from work, respectively. These associations translate in many years of working life lost as well as high indirect costs to society.

Early retirement is likely to decrease the income and wealth of the individual, places a burden on government due to the lost income taxation revenue, the net increase in benefit retirement payments and translates into a great burden to society due to its concomitant productivity loss. Early retirement has become a serious problem among the so-called developed countries, which have continued to observe an increase in the overall life expectancy and in the share of the population that is made of economically dependent elderly people. The old-age dependency ratio is progressively growing and early retirement worsens this sustainability problem of modern societies. Portugal already has one of the worst old-age dependency ratios in Europe and therefore in-depth knowledge about this issue is crucial for the future of our country. In addition, it might also represent a case study and a useful reference for policies to be undertaken elsewhere, in countries similar from a socioeconomic and epidemiologic perspective, such as other Southern European countries. Nonetheless, given the complexity and the multifactorial nature of this social concern, it might be impossible to have an absolutely identical paradigm across all different contexts and environments. Learnt lessons from elsewhere are important and worthy of attention, but should always be taken carefully. Moreover, different studies, which necessarily have different designs, quality and data sources will deliver further heterogeneity on this subject.

Many factors may rush retirement decisions in individuals. They can be of completely dissimilar nature. Some are financial whilst others are health-related. These determinants may influence positively or negatively and certainly may interact and depend on each other. A given disease, for instance, may push patients away from the labour market within a specific legal and financial framework, whilst being innocuous in another environment.

Ill-health determinants are of particular interest. Most disabling conditions may have their progression deferred. Early and effective diagnosis and treatment may significantly improve patients' work participation. On the other hand, universal health coverage allows interventions regardless of socioeconomic status, which is something untrue for other factors. Also, many diseases (e.g. cancer) are more valued by society and employers than other factors (e.g. marital status or lifestyle factors), causing more understanding and potentially more action to help sick employees willing to remain at work. Undoubtedly, this latter consideration does not apply to all diseases, particularly those still stigmatised by society, such as AIDS or mental diseases. Finally, many interventions may target illness even at its later stages. In this respect, ergonomic work adaptation to support disabling patients is a growing field. The obvious potential economic gain makes research in this area particularly appealing for countries concerned with long-term sustainability issues. However, in general and mostly due to the recognized complexity of this subject, it has been difficult to draw any satisfactory conclusions concerning specific interventions with the aim of increasing work participation.

The impact of ill-health on premature retirement has been observed in many diseases, such as cancer and heart disease. RD, as a whole, are widely prevalent and disabling. Many studies have been performed in order to assess the relationship between exposure to these disorders and premature job loss. The heterogeneity around this presumed causal chain makes it hard to reach a final conclusion, namely by exactly defining the strength of the association. For example, rheumatic patients tend to be less educated and to be of lower socioeconomic status. This fact *per se* influences the likelihood of being or not in the labour market. This is why it is so important to consider several potential confounders. Interestingly, work itself may harm the individual and cause or deteriorate musculoskeletal symptoms, meaning that for some cases RD are an intermediate step between being at work and exiting from it. For instance, there might be a bidirectional relationship between OA and work. On the one hand, several aspects of physical workload have been identified as risk factors for developing knee and hip OA (e.g. kneeling work positions, jumping, and heavy lifting).[209] On the other hand, people who have OA may perceive difficulties in performing work. Regardless the exact origin of a given disabling RD, these are medical conditions of great interest for this type of research. RD

progression can be adjourned in most situations and certainly its impact in work participation. Without any doubt RD are a very good model for research and interventions aiming to diminish early retirement.

This work has used two primary large nationwide datasets: First, the National Heath Survey of 2005-2006 (INS); and secondly, the Portuguese epidemiologic study on rheumatic diseases of 2011-2013 (EpiReumaPt). Both enabled a fruitful research considering several possible confounders of different nature, whilst at the same time granting national representativeness from their samples (external validity). Over half a decade separates these cross-sectional surveys, a condition of added value to this analysis, because it allowed addressing the same topic in different time points associated with dissimilar macroeconomic and social contexts despite the same geographic and cultural references. Of special note, INS refers to a period in time before the Portuguese sovereign debt crisis, which brought socioeconomic changes, while EpiReumaPt refers to a posterior moment. It is therefore interesting, for example, to observe how the association between RD and formal premature retirement has evolved through this austerity period. Other differences can be emphasized. For instance, within these time points the National Program Against Rheumatic Diseases 2004-2010 was implemented in our country,[49] a national effort and contribution for the worldwide Bone and Joint Decade 2000-2010 endorsed by the WHO,[10] which is expected to have helped referral and treatment of RD. Also, access to specific rheumatic innovative drugs (e.g. anti-TNF therapy) has emerged substantially, thereby producing better disease control and less progression of particular disabling forms of RD, such as RA. Using both surveys data did not only serve the purpose of comparing different temporal points, but also, and perhaps more importantly, allowed to look at the same problem from a different angle. In fact, while INS was an appropriate data source as a first approach to understand the relationship and impact of RD on early retirement (after adjustment to general cofactors), EpiReumaPt allowed the analysis to use some RD-specific data (e.g. KOOS) and some other information specific to the adopted model (e.g. pain, disability and RD-caused early retirement). It also allowed narrowing the research on a particular prevalent and disabling form using clinically confirmed data (i.e. OA).

This thesis uses self-reported and clinically confirmed data, from which several advantages and disadvantages may be listed. Clinically confirmed data is obviously a great source of valid information. It refines the case definition of the studied exposure variable and may deliver RD-specific clinical data of significant relevance. However, taking in consideration the ultimate goal of this research, which is to provide practical and lean orientation to identify and act upon employees at-risk, clinically confirmed data may not be always the most adequate starting point, particularly for regions and people with difficulties accessing specialized medical appointments (e.g. manual workers from rural areas of Portugal). Thus, one cannot exclude the usefulness of self-reported data, in particular for some of the types of subject under analysis. Self-report is one of the most widely used methods of collecting information regarding individuals' health status and utilization of healthcare services.[210] Several cost-of-illness studies on RD have used self-reported data in the past.[75,79,211,212]

The relatively recent development of patient-reported outcomes throughout many fields of health research also reveals the recognition of the importance of self-reported data. Certainly, this sort of data may be vulnerable to misclassification bias, but in the case of this study, self-reported RD is more likely to comprise a subset of more severe RD cases (possibly underlying the higher HAQ scores and worse EQ-5D and SF-36 scores observed in this group when compared with the whole EpiReumaPt's clinically confirmed RD group. Appendix 2), rather than including non-RD cases (over 94% of those who self-reported RD in the EpiReumaPt sample had their RD diagnosis clinically confirmed by the rheumatologists). Consequently, self-reported data, in particular the one used to define the exposure variable of this study didn't include too many false positives (i.e. self-reported RD has high specificity [79.9%] and very high positive predictive value [94.9%]. See Appendix 3) and may in fact represent a reliable proxy of disabling RD, predominantly composed by more severe and advanced disease stages (of note, it delivered many false negatives and therefore relatively low sensitivity [49%] and very low negative predictive value [17.1%] [Appendix 3] because it misses many less severe RD forms otherwise identified by rheumatologists in the last stage of EpiReumaPt, who found a prevalence of over 73% of RD in this age-group).

Most importantly and as already alluded, from a more pragmatic point of view and given the explored field, self-reported data can be of special interest for policies targeting early retirement on the grounds of ill-health. For instance, it may encourage fast and easy identification of vulnerable RD employees. Clinical confirmation of RD diagnosis might happen too late for any action aiming to avoid exit from work. Thus, despite the need for a final RD diagnosis by a rheumatologist, self-reported information about RD should be considered prior to further and more complex measures. It may well trigger a faster and more efficient way to detect at-risk RD employees than what can be expected from the national health system as it is, where gaps in the identification and treatment of RD have been observed.[84,85] Despite all this, obviously we have to recognise the flaws and limitations of self-reported data when taking conclusions from this study. In addition, we considered important to use clinically confirmed data when dealing with specific RD forms, such as OA. OA is a frequent and sometimes misdiagnosed condition. It can be easily confused with other conditions by the patient, hence further endangering self-reported data. From an interventionist viewpoint, this disease might be detected earlier and managed by the general practitioners. Therefore, widespread access to diagnosis and treatment to avoid work disability can be achieved much easier when compared with many other rheumatic forms.

This research was based on large and representative samples of the Portuguese population approaching the statutory age of retirement and suggests an association between RD and early retirement. RD play a key role in pathways of early retirement – first, at younger ages, it seems to affect predominantly more temporary forms of exit from work, such as unemployment and then more permanent forms, such as official early retirement. In 2005/2006, using the INS database we verified that almost half of the studied age-range of the Portuguese population (45.1%) was out of work (since then this figure worsened. In the EpiReumaPt 2011/2013 we observed more than half of the population in this situation). This group was more likely to have a RD than the remaining population (38% vs. 30%, respectively; p=0.02). In fact, in the INS survey more than half (52.6%) among those who self-reported to be suffering any kind of RD were not employed. It is true that RD itself may be associated with occupational risk factors (e.g. low educational level and comorbidities), however the relationship between RD and early exit from work

remains statistically significant when controlling for relevant confounding (OR 1.31; 95% CI 1.12-1.52). Not surprisingly, in this study we also observed other factors linked with the studied outcome. Lower educational level and poorer household income are independently associated with early exit from work. The latter does not remain significantly associated to premature retirement when controlled for other cofactors. Anyway, conclusions about this cofactor should be taken carefully because the outcome (early retirement) itself directly and immediately interferes with it, since at least one of the household members had the income reduced due to early retirement penalties. Interestingly, comorbidity seems to play a more significant role in early retirement, rather than the more general outcome of early exit from work. In the EpiReumaPt survey almost half of those who retired prematurely said it was due to disease. Major comorbidities may be more influential in permanent forms of work withdrawal (i.e. early retirement) than in temporary ones (i.e. unemployment). It makes sense to expect that comorbidity may be less influential in the retirement pathways that are strongly dictated by external factors, such as the case of unemployment. This observation is corroborated by previous research.[126,165] The female gender appears to have a negative effect on early exit from work, while male gender is more associated with early retirement and unemployment. This difference may lay on the fact that homemakers (mainly women) were included in the broader group of early exit from work. If this is the case, among the employed population, men are exiting work more often than women. Indeed, using data from the EpiReumaPt survey we observed a worse effect of male gender in official early retirement (although female gender was more associated with early retirement due to RD).

In spite of the differences of the time points of both surveys, our analysis using EpiReumaPt dataset retrieved results generally consistent with the INS ones. In particular, we observed a similar strength of association between RD and early retirement (INS: OR 1.24; 95% 1.01-1.52 vs. EpiReumaPt: OR 1.37; 95% CI 1.01-1.84), which is similar to what was previously found in other studies, such as Ranzi TL *et al.*[127] and Alavinia SM *et al.*,[126] but somewhat lower than others, like Schofield DJ and colleagues, who calculated an OR of 3.06 (95% CI: 2.52-3.73) when testing the association between arthritis and related disorders with being out of the labour force, however the adjustment was only done for age-group and sex and the

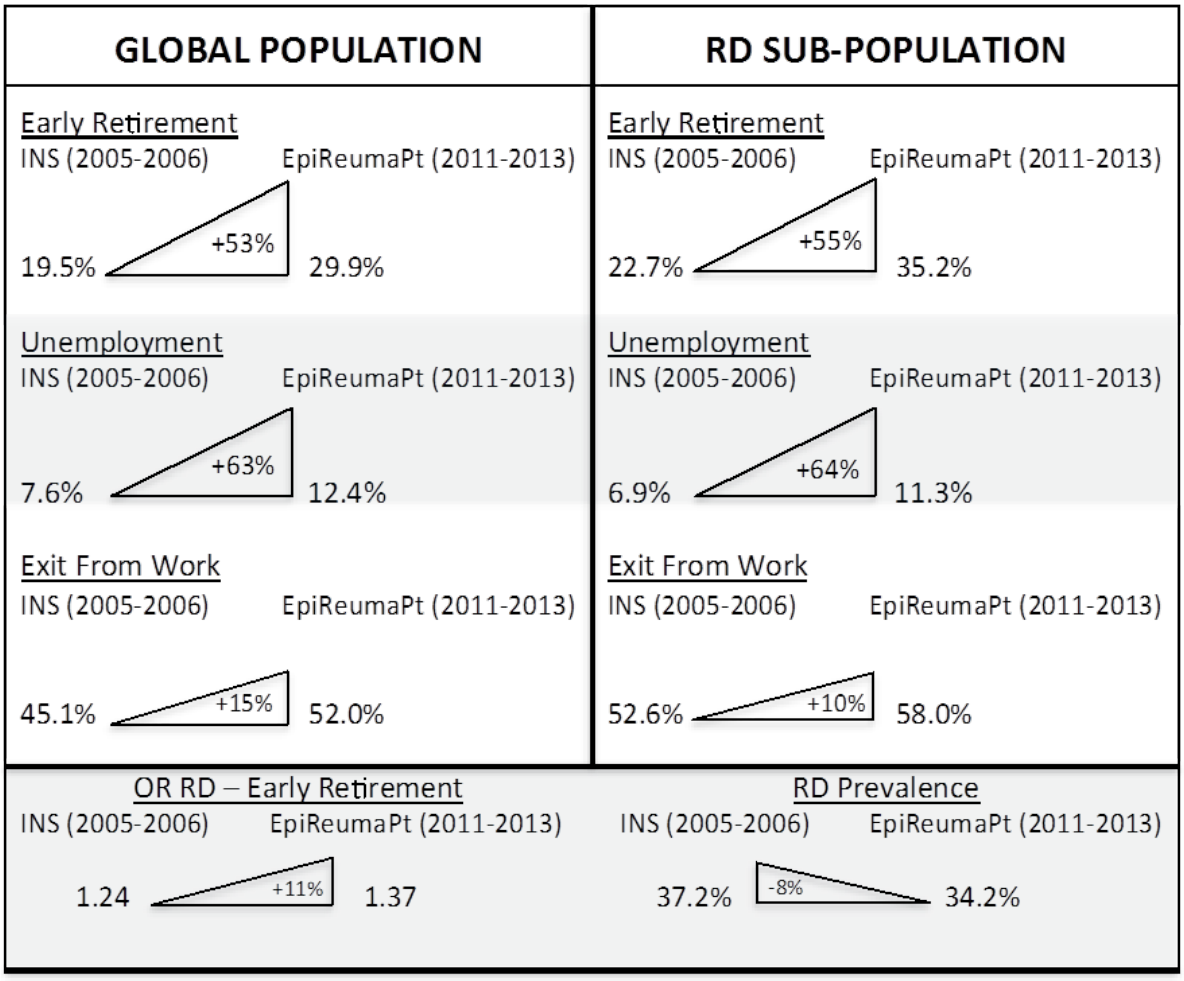
outcome was broader than strict early retirement.[162] Also, as previously discussed in Section A, a lack of association between RD and job loss was found in some studies. For instance, Lund T and Csonka A found that although the initial univariate analysis confirmed the association between MSK symptoms and work disability, statistical significance was not reached in the multivariate analysis. This contrast with our findings might be explained by geographic (Denmark) and temporal (1997) differences, as well as the definitions used for the exposure (MSK symptoms), the outcome (work disability, defined as receiving a disability pension or being on long-term sick leave) and the adjustment, which used distinct cofactors (including the company size and belonging to the public or private sector).[154]

Alike the strength of association, we found only a slight difference on the self-reported RD prevalence (INS: 37.2% and EpiReumaPt: 34.2%.[vii] Figure 9), which might be due to how self-reporting was collected (i.e. wording of questions used in each survey. Section A – Brief Methodology – Case Definitions), rather than a result of a hypothetical epidemiological change occurred meanwhile, within the studied age-range.

However, in the EpiReumaPt study we didn't find an independent association between RD and early exit from work (*lato sensu*).

[vii] *In the last Portuguese national health survey (INS 2014) the proportion of people aged 45-54 years self-reporting arthritis was 18.7%, while 38.8% for those aged 55-64 years.*

Figure 9 – Comparison between main findings of INS and EpiReumaPt



Dedicated longitudinal data would be essential to better understand what exactly had happened, but there could be several non-mutually exclusive reasons for this scenario, namely:

1) In the recent years, some factors (e.g. those more susceptible to the sovereign debt crisis) may have become more relevant in the causality of general exit from work (thereby taking over the role of RD in this outcome) while perhaps less influential in official retirement.

2) Macroeconomic and social changes might undermine this as well. For instance, unemployment rates were up considerably in Portugal and Europe regardless of any individual characteristic, lowering the RD effect on early exit from work.

3) More RD patients may have been allowed to move directly to early retirement (bypassing other temporary forms). This would result in the observed increment on the strength of association between RD and early retirement while, at the same time, a decrement in the association with exit from work (which includes all pathways, thereby "diluting" the effect of RD on early retirement).

4) The pool of RD patients found in 2005/2006, who were already out of work, might have moved to official retirement in greater extent than the influx of new RD patients exiting work through temporary pathways.

These last 2 potential reasons could be explained by anticipated decisions of early retirement specially among those older and more vulnerable, such as RD patients, in order to avoid the foreseen rise in the official retirement age (i.e. 66 years old, implemented in the meanwhile), the expected future penalties and worse eligibility criteria. Our data supports this hypothesis because there was a sharp increase in early retirement from 2005-2006 to 2011-2013 for the whole population (+53%[viii]) and even more when specifically analysing the RD subpopulation (+55% from an already high "baseline". Figure 9), but the opposite was seen when looking for overall exit from work, since the increase in the global population (+15%) was higher than in the RD subpopulation (+10%). Additionally, we verified that mean retirement age due to RD has recently increased, especially in the last 5 years, and so did the prevalence of early retirement in the oldest age-group (60-64 years old) in proportion to the remaining age-groups, something that didn't happen for general exit from work in the RD subpopulation (Table 3).

In the absence of more data, it is difficult to understand exactly what has occurred; likely all the above hypothesis could partially explain it. However, the recent sovereign debt crisis, which likely puts more pressure on those more vulnerable, and the subsequent modifications in the laws and rules of retirement, surely had a role in the evolution observed.

[viii] *According with oficial data (Eurostat/INE) anticipated old-age pensions have increased by 40.3% between 2006 and 2012 in Portugal.*

Table 3 – Employment Status According to Age-Groups found in INS and EpiReumaPT (%)

	INS					EpiReumaPT				
Age- Group	Global	Retired	Retired +RD	Exit from Work	Exit from Work +RD	Global	Retired	Retired +RD	Exit from Work	Exit from Work +RD
50-54	36.5	12.5	9.9	22.8	17.0	34.8	9.2	8.4	22.3	18.8
55-59	33.8	30.4	30.4	34.2	34.4	33.1	28.4	29.3	30.8	32.2
60-64	29.7	57.1	59.6	43.0	48.6	32.1	62.4	62.3	47.0	49.1
Sum	100	100	100	100	100	100	100	100	100	100

Another possible reason could be based on overall worsening of the disease control of rheumatic patients in Portugal and consequently poorer physical disability, pushing RD patients into permanent forms of early retirement (of note, the HAQ scale is absent in the INS data, therefore comparisons between surveys about physical function is unfeasible). Empirical knowledge weakens this hypothesis, because in the last decade RD patients had more access to innovative drugs and to primary and secondary care, following, for example, the primary health care reform initiated in 2005 in our country[213] and the implementation of the already mentioned National Program Against Rheumatic Diseases (2004-2010).[49] We also don't consider plausible to expect that working conditions in Portugal deteriorated enough to lead RD patients into formal early retirement faster than before. Nevertheless, our data is insufficient to categorically dismiss this hypothesis. Lastly, it cannot be overemphasized that comparisons of the results obtained in these surveys should be done carefully, given that differences may lay on their distinct nature, as explained before. It is also worth noting that this evolution applies to overall self-reported RD. It doesn't apply to specific forms of RD. In fact, as further explained in more detail, we observed that OA is associated with early exit from work while it is the opposite with official early retirement (of note, no comparison with INS 2005-2006 was possible to be done specifically for OA due to lack of such information in this survey). This might mean that forms of RD that are more widespread and/or less valued by society and employers, such as the case of OA, were unable to have the same access to early retirement as the self-reported RD group, which, as previously explained, probably includes more advanced and disabling RD patients.

The EpiReumaPt study, which directly inquired the participants about the reasons of early retirement, revealed that almost half of early retirements were on the grounds

of ill-health and about one third of these were specifically due to RD. Thus, 3.9% of the Portuguese population aged 50-64 years old (equivalent to 66,953 individuals) self-reported RD as the main reason for early retirement. Despite the increase in the prevalence of permanent early retirement in RD patients, our data suggests an improvement regarding the average age of retirement due to RD. Thus, a positive trend on the mean age of early retirement caused by RD was seen, even though this situation varies from region to region of Portugal. For instance in the Lisbon region, regardless of having a higher frequency of early retirement due to RD (4.3% versus the national average of 3.9%) it has a higher average age of this type of retirement (58.6 versus the national average of 54.8 years old).[214]

A lot remains to be understood about the underlying rational for this specific improvement and it goes beyond the aims of this study. However, it would be interesting to know if, for example, early retirement caused by RD is being artificially postponed in some areas (e.g. excessive penalties unaffordable for those with lower income) or if, as detailed before, in the recent years older RD patients found opportunities to retire, anticipating imminent harsher retirement conditions, something that couldn't be easily attained by younger RD patients. In addition to this, structural policies might have taken place in order to avoid RD disability and promote job adaptation, keeping RD patients as much as possible in the work place. However, the recent sharp increase of early retirement makes this option less plausible and to our knowledge no noteworthy initiatives related to job adaptations for RD patients were implemented in our country.

Lastly and still regarding the observed regional differences, one cannot discard the noticeable evolution around the overall management of RD in the last years, but also cannot ignore enduring geographic inequalities. The observed regional differences may indeed reflect horizontal inequity in the access to diagnosis and treatment. Consistent with this observation, Alentejo, likely to be the region with worse access to RD treatment, scored worse than the national average on self-reported prevalence and age of early retirement due to RD.[214] It's worth taking in consideration that poor access to treatment not only precipitates productivity costs, but also may lead to higher direct costs following the progression of an uncontrolled disease. These sort of economic consequences were estimated on the second part of this study.

Still using the INS dataset, we estimated that RD-related productivity losses due to early exit from paid employment were potentially associated with annual costs between €367 million (if considering strictly official retirement) and €650 million (in the case of broader job loss). Thus, considering the timeframe of the survey (2005/2006), this type of costs amounts up to approximately 0.4% of the national GDP in 2005. However, when access to the EpiReumaPt database was obtained we had the opportunity to achieve more accurate and recent results. Thus, we estimated that early retirement self-reportedly to be attributed to RD is potentially associated with an annual cost of up to €910 million in Portugal, which translates to approximately 0.5% of the national GDP in 2013, which seems to be in line with the GDP share of other countries.[72,75,215] In this study, we used a different outcome compared with the one used for the INS dataset (i.e. early retirement attributed to RD according with the participants' own report), nevertheless it is important to scrutinise these two results together. No significant variations at the epidemiologic level were seen and, as already noted, the strength of the relationship between this health condition and general early retirement progressed modestly (note: some cofactors used in the multivariable regression are different between surveys. This itself may drive the difference in the respective ORs). However, from a strict economic perspective the situation appears to have worsened, considering the indirect costs in relation with the GDP and the indirect cost per RD patient. This difference may result from several causes. Early retirement has increased substantially (note: comparisons about retirement due to RD are unattainable, due to lack of such information in the INS survey) so did productivity unit values (+25-30%). Mostly, and already highlighted, the EpiReumaPt study participants were for the first time directly asked whether they had retired prematurely because of RD. The RD effect on early retirement was directly assessed, while with INS we had to use the estimated effect through logistic regression and PAF in the general early retirement. Even using a more conservative approach (i.e. considering other competing risk factors for RD-caused early retirement) the EpiReumaPt obtained indirect cost per RD patient is substantially superior to the one using INS (€1359 vs. €504, respectively). However, if we are to use the same exact outcome of general early retirement in the EpiReumaPt database and the same PAF methodology as INS, we observe an increase in the total annual indirect costs and in the cost per RD patient (€550M and €982, respectively. Data not included in the article and only presented in

Table 4 for comparison purposes with the INS results), but both results are more aligned. It is counterintuitive to verify higher indirect costs when we consider the outcome of RD-related retirement (i.e. outcome “b” in Table 4), which is a subset within all early retirement (i.e. outcome “a” in Table 4). This has to do with the contribution of RD to each of the embraced outcomes. While in the retirement caused by RD the consequent indirect costs are all or almost all credited to RD, in the general retirement there are competing risks and therefore only a small fraction of indirect costs can be attributed to RD (given by the resulting proportional change in the probability of early retirement after a counterfactual exercise where the presence of self-reported RD is artificially eliminated from the sample, which is the essence of the PAF methodology, a common approach of cost-of-illnesses studies). In addition, when indirect costs are calculated based on the general retirement an underestimation might occur, since there might be an improvement on RD symptoms after job loss (thereby reducing self-report of RD and artificially “hiding” its previous effect on retirement decisions).[216] Although in Portugal the retirement decision by itself doesn’t seem to affect health status.[193,217,218,219]

All this reemphasizes the importance of the more accurate outcome given by the EpiReumaPt study and also makes the point that, even considering true variations throughout time, we have to acknowledge that INS indirect costs were likely to be an underestimation of the real economic impact of RD on early retirement. We cannot also rule out an overestimation on the calculation of costs following retirement due to RD captured in EpiReumaPt. Nonetheless, regardless the exact amount of indirect costs associated with this productivity loss, our research makes it very clear about how considerable they are in Portugal, to an equivalent of up to 0.5% of the GDP. This fact becomes even more pronounced after examining the specific RD form of OA, as further discussed below. As explained, comparisons with the available literature are hampered due to several reasons, including adopted definitions of the exposure and dependent variables, as well as the used methodologies. However, our high estimates are in line or even inferior to the ones found in the literature.[72,74,75,79]

Table 4 – Indirect Costs Obtained for Self-Reported RD and Clinically Confirmed OA

	Self-Reported RD						Clinically Confirmed OA		
Data Source	INS			EpiReumaPt			EpiReumaPt		
Outcome*	a	b	c	a**	b	c	a	b**	c
Total Annual Indirect Costs	€367M	NA	€650M	€550M	€761M - €910M ***	NA	NA	€237M	€656M
% GDP	0.2%	NA	0.4%	0.3%	0.5%	NA	NA	0.1%	0.4%
Cost per RD Patient	€504	NA	€892	€982	€1359 - €1625	NA	NA	€467	€1294

**Outcome: a) Early Retirement; b) Early Retirement due to RD; c) Early Exit from Work*
***This data is not presented in the articles. It was included here for comparison purposes.*
****Another alternative for this estimate would be considering in the calculations only those RD cases clinically confirmed. In this case the estimate decreases to €747M.*
GDP, Gross Domestic Product for the respective year; M, Millions; NA, Not Available; Osteoarthritis; RD, Rheumatic Diseases.

We have used EpiReumaPt data to ascertain the healthcare resource utilization made by different groups according with their working status and RD presence. Both RD and early retirement were associated with greater costs of this nature. Consequently, the RD patients who also retired early have the highest consumption among all analysed groups. Dedicated research could specifically study this phenomenon. Nonetheless, it becomes quite obvious that RD patients who are work disabled should be prioritized and well managed so that social security and NHS expenditures can be adjourned. In addition to this, early identification of disabled RD patients is of paramount importance. We have seen a strong association between disability and early retirement, which is consistent with our conceptual model (Figure 7) and with some previous studies. [197,198,199] For instance, Lacaile D and colleagues have found an increased risk of no paid work due to RA in people with higher HAQ (OR: 1.96; 95% CI: 1.2-3.3).[197] Indeed, we observed a cumulative risk of early retirement when a given RD patient already had high levels of HAQ. This reinforces the need to segment RD patients according to disability levels because it is a potential straightforward method to set distinct levels of work withdrawal risk and healthcare resource consumption. In addition to this, identification of other vulnerable groups can be very useful from a policy perspective. In the first work done with INS we emphasized the risk among manual workers, who are exposed on average to harsher working conditions, and detailed the discussion around a particular potential at-risk group composed by manual RD female workers from the North of Portugal. This resulted from the examination of specific characteristics and their association

with early exit from work (of note, when considering narrowed forms of work withdrawal, the North region is not performing worse than the national average). In-depth analysis of specific populations can be very useful for the decision-making process around early retirement. Policies should prioritize special risky groups, while being flexible enough to go beyond generalizations. When it comes to such multifactorial problem nothing is absolutely inevitable and predictable, therefore segmentation based on risk factors can be a relevant exercise but should not dictate "blind" policies disregarding the individual variations. In fact, as detailed in the third part of Section B of this thesis, this is one of the reasons why much of the research dedicated to interventions aiming to reduce early retirement are of qualitative nature, using for example interviews or focus groups to understand the perspective of the individual and going beyond a strict epidemiological vision and "blind" simplifications drawn from the community. This can also explain part of the general lack of success verified in the trials testing vocational rehabilitation programs, which necessarily had to be conceived from generic epidemiologic knowledge.

Still regarding subgroup breakdown, the asymmetric gender impact on the different forms of early retirement and due costs is very clear. Females tend to be more prone to the most and the less specific studied outcomes (i.e. early retirement caused by RD and premature exit from work), while males are more susceptible to the in-between forms (i.e. official early retirement and unemployment). RD are more frequent in women and this certainly partly explains the retirement pattern, but it doesn't explain everything. First, female gender remains statistically associated to early retirement caused by RD even when adjusted to other risk factors (*ceteris paribus*), including RD itself; second, other factors associated with women can additionally push them out of the market, even when RD is the identified main cause. Disability can be the most obvious of those factors. Indeed, we observed more disability in females versus males within the self-reporting RD group.

In the second article reporting RD indirect costs associated with early exit from work, we could verify that females were responsible for about 60% of these costs, while in the article which measures more specifically the indirect costs of RD-related early retirement, that share rises to 84%. This could have been the result of a possible reduction in the gender wage disparities between the time period of INS (2005/2006) and the one of EpiReumaPt (2011/2013) that could lead itself to a higher share from

females, but unfortunately in the last decade we did not observe such trend in the studied age-range. Therefore, this cannot explain this increase in the relative female gender impact. We cannot disregard that the different methodological approaches may underlie some of the changes in gender share of indirect costs. For example, by using a similar method based on PAF the female share of indirect costs of early retirement due to RD becomes lower than 84% (i.e. 79%). Nevertheless, the main reason is expected to lie on the studied outcome. It is true that females are more likely to be out of work than men and that leads to their higher contribution (female gender OR: 2.12; 95% CI 1.80-2.51), but this includes early retirement pathways, which actually are more influenced by male gender, as already said. However, early retirement specifically caused by RD is much more likely to occur in women (female gender OR: 4.12; 95% CI 2.04-8.31), thus the disproportional contribution of female gender in this case. Also, we cannot rule out the possible changes that might have occurred between the two surveyed time points. Early retirement in Portugal might have become restricted to more disabled patients and, as explained before, RD female patients have higher disability than male ones, which is in agreement with others' findings.[220,221,222] This more severe functional condition might *per se* push females out of work more frequently within a social system less willing to accept early retirement of mild health conditions. We could also speculate if couples, especially within the recent austerity environment, are favouring RD males to remain at work, because they have on average a higher salary, making the overall household income less vulnerable to the respective early retirement penalties. If true, this situation exacerbates the gender asymmetry on indirect costs. Some literature suggests that couples may indeed coordinate their decisions and the partner may influence the choice of leaving the labour market.[147,148] In this research we didn't find an independent association between marital status and the likelihood of being early retired, except when using the OA model. It is true that some studies have shown an effect of marital status, but the employment status and probably the income of the partner may play a bigger role on this regard. We could not access this level of information but further research may address the household and the family context in the retirement decisions of their members.

As a last remark around the gender asymmetry on indirect costs, if gender wage disparities had been reduced since 2005 the estimated indirect costs would have

been even higher. In fact, we estimated that if we were to assume productivity values similar to those of men the indirect costs estimate would raise by about 30%. Further research is necessary to understand how these costs will evolve in the coming years as a function of the expected evolution of gender disparities.

The EpiReumaPt dataset made it possible to test the association between pain, disability and early retirement, through the use of appropriate instruments (e.g. HAQ). Indeed, we have verified a strong association between pain, disability and early retirement, building further on the adopted conceptual model that gave rise to this study. Persistent musculoskeletal pain is a unifying characteristic across the vast majority of rheumatic conditions. It is particularly common in self-reported RD and might actually lead RD patients to better remember and to state suffering from a RD. We studied pain in more detail using OA, a rheumatic clinical condition particularly distressed by pain.

RD patients have functional limitations that may translate into work disability. We observed an additional likelihood of early retirement when a given RD patient had higher levels of HAQ. In fact, a “dose-dependent-like” (biological gradient) relationship was observed, with an almost linear correlation between levels of disability and the probability of early retirement. Furthermore, when comparing individuals with same HAQ scores, the ones with self-reported RD were more likely to be retired. It may be that besides the main causal chain between RD and retirement, which includes disability as a main intermediate step, there might also exist an additional “route” independent of physical disability. Understanding this potential alternative causal chain was beyond the scope of this research, but it may involve psychological factors (mental disability) known to be associated with RD. Some RD patients may be vulnerable, not only from a physical point of view, but also from a mental one (e.g. chronic anxiety and depression), which itself may predispose them to suffer an additional retirement risk.

All this reinforces the importance of the used proxy of self-reported RD, because this group not only has higher physical disability (HAQ scores) against the clinical confirmed RD population (a broad group composed by many RD forms at different stages, including non-disabling ones – within the studied age-group, over 73% of the people had some form of clinically confirmed RD); but also higher levels of mental

disability (e.g. 29.0% of self-reported prevalence of mental diseases in the self-reported RD group compared with 19.7% in the clinically confirmed RD patients), added to the fact that RD-related retirement does not seem to be entirely explained on the grounds of physical disability. Therefore, this further justifies why self-reported RD should be thoughtfully considered. Identification of self-reported RD people shall trigger further needed actions (e.g. diagnosis done by a rheumatologist) and disability assessment. At least from a physical standpoint and since the HAQ assessment is quite simple and inexpensive, employers could periodically survey employees regarding their level of disability. This could be a fruitful proactive investment particularly for manual workers.

Studying clinically confirmed OA allowed addressing specific fragments of the adopted etiological model in more detail, such as pain and disability. Unsurprisingly, we verified that Portuguese OA patients consistently reported more persistent pain than others without the condition. In fact, pain is one of the symptoms that should validate the clinical diagnosis of OA. It is the most disabling manifestation of this RD. Chronic pain has been shown to be a major contributor to increased healthcare utilisation, reduced labour productivity, and consequently large direct and indirect costs. Another study has estimated that the total annualised chronic pain costs in Portugal amounts to €1,977 million for the total annualised direct costs, €2,646 million for indirect costs, and €4,612 million for the total costs. These estimates correspond to 1.2, 1.6, and 2.7% of the Portuguese annual GDP in 2010, respectively.[223] Due to the high prevalence of OA in Portugal (Knee OA: 12.4%; hand OA: 8.7%; hip OA: 2.9%)[23] and its increased incidence of persistent and disabling pain, it becomes quite obvious that pain control in OA patients is crucial, not only for the individual, but also for the society as a whole. However, many OA Portuguese patients do not experience adequate pain control.[224,225] Along with the available literature, our research highlights the potential social consequences of inadequate management of OA, specifically when it comes to pain relief.

Also, and consistently with the previous discussed results in self-reported RD, more impactful forms of OA (i.e. worse symptoms measured by KOOS subscale scores and/or disability measured by HAQ) were at the highest risk of premature work loss. Thus, OA fulfilled the promise of being an appropriate RD to test the adopted etiologic model. Interventions may target any relevant intermediate step (as earlier

as possible) in order to break the chain between OA onset and work withdrawal. Depending on how soon and at which level one desires to act upon, these interventions may target directly pain and inflammation (e.g. analgesics, NSAIDs and knee arthroplasty) and/or the work situation, such as adapting hours, tasks, workplace, and the use of aids, as further described in the third part of Section B of this thesis. By doing so, many years of working life lost may be spared.

As before with self-reported RD, we estimated many years of working life loss attributable to OA and even a higher number of potential years to be lost if no return to work happens until the official retirement age in the OA population. As with RD, this data highlights the need to also consider interventions fostering return to work, whenever possible. The overall inactivity ratios, measured by the time the individual stayed (and potentially will remain) out of work as compared with its potential working life span, are also elevated. On average up to almost a quarter of the working age-range is lost in this group of early retirement OA patients, which translates in large indirect costs to society.

An annual cost of €656 million (i.e. 0.39% of 2013 GDP) attributable to OA through early exit from work was estimated. Once again the female contribution was meaningful (~62%) although the cost per OA male patient is much higher, mainly due to the fact that wages are larger in men.

No measurement of indirect costs was done specifically for the official premature retirement route because we didn't find a significant association of this outcome with OA. OA seems instead to drive the labour force out of paid employment mainly through unemployment, which may prevail over official early retirement (competing outcomes), especially in the youngest ages. Notwithstanding, this doesn't fully explain the lack of significant relationship of OA with official retirement, because long-term unemployment can usually be converted into premature official retirement (as a matter of fact in the first figure of the forth article it is possible to observe the interchangeability between unemployment and retirement rates, in which the former seems to be "overtaken" by the latter. Of note, the lack of significance in the multivariable regression with official retirement as the outcome may also be partly due to less statistical power compared with the analysis of all sorts of exit from work, which necessarily accounts for more events to be evaluated). As already discussed,

further research should investigate if policies are somehow restricting early retirement in these patients, on the grounds of a less valued RD form. Alternatively, other causes may prevail, such as the rejection from OA unemployed patients to retire before the official age. Regardless of the cause, unemployment is a route of special interest that should be tracked more closely in future studies. It is possible that OA patients are perceived by employers as less fit for work, therefore being first on the layoff list, while at the same time not disabled enough to be eligible for early retirement (although mean HAQ levels are superior on those suffering from OA than those who self-report RD: 0.64 vs. 0.57, respectively). If this is the case, increases in pension age in Portugal, as with many developed countries, may exacerbate this situation. OA is a paradigmatic example of the need to engage employers in integrated actions to accept and help, whenever possible, patients to remain productive at work.

It is difficult to compare the indirect costs obtained for clinical confirmed OA versus self-reported RD. On one side, if we want to compare results from the same data source and timeframe then the occupational outcome is distinct (Table 4); on the other, if we want instead to analyse OA in relation to RD, the case definition is of a different nature, as mentioned before (clinically confirmed data versus self-reported data). Therefore, comparisons, if any, must be carried very carefully.

It is true that OA indirect costs look very high when compared to the results of self-reported RD, especially those obtained with the INS dataset (Table 4), which is not the case when comparing to the YWLL findings (YWLL due to RD retirement in the overall self-reported RD group was estimated to be 389,939, while in OA it was 74,957). In agreement with many previous studies of the same nature (i.e. cost of illness studies), our methodological approach to measure the economic impact of early exit from work was based on PAF, which takes into account both the strength of the association between a risk factor and the outcome and the prevalence of that risk factor in the population. Even though self-report of RD was more frequent in the INS database (37.2%) than what was found in the clinically confirmed OA in EpiReumaPt (18.6% of knee OA, which was the location used to calculate indirect costs, given the lack of association of hip and hand OA), the strength of association was much lower (OR: 1.31) than the clinically confirmed knee OA (OR: 2.25).

These imbalances partly explain why results in the end were so similar, but a number of other factors might be playing a role as well, such as the already mentioned increase in the unit values and the frequency of the outcome itself (2005-2006: 45% vs. 2011-2013: 52%). In addition, while OA is undeniably one of many RD forms, clinically confirmed OA cannot be seen as a subset of the self-reported RD, because the latter itself is a subset of the much broader clinically confirmed RD group. In the EpiReumaPt database, within the studied age-range of 50-64, we found a prevalence of over 73% of patients with at least one clinically confirmed RD. This group is mainly composed by low back pain, periarticular disease, OA and OP, almost all of which (i.e. all except OA), were not statistically associated with job loss. This might actually be the main reason as to why we didn't find any association between clinically confirmed RD and any sort of exit from work (i.e. even if some RD forms, like the case of OA, have an effect it is attenuated within this large and hugely heterogeneous group mainly composed by less disabling RD forms, which are not strongly related with premature exit from paid employment[ix]). This lack of association made it impossible to measure indirect costs for the whole clinically confirmed RD group, which certainly would have made much more sense to compare with the herein presented results for clinically confirmed OA. Undoubtedly, other disabling RD forms should be further analysed. One limiting step to do so is not having enough statistical power to perform multivariable regressions due to the relatively small sample size of less frequent RD forms in this age-range. For example, despite being out of the scope of this thesis, we explored the relationship between RA and early retirement. With our adopted age-range we couldn't reach any statistical significance when testing this relationship, however, once the age restriction was widened to adults bellow retirement age (i.e. 18-65 years old), statistical significance was attained. Hence, there seems to be a relationship though difficult to explore given the low sample size (in the EpiReumaPt sample only 23 people aged 50-65 were diagnosed with RA versus 518 with OA). RA is particularly interesting to explore given the already mentioned economic impact. Maetzel A *et al.* observed that *per capita* indirect costs related to RA were up to five times higher than indirect costs incurred by patients with OA.[226]

[ix] *In fact, we tested the association of clinically confirmed RD according with different levels of disability, and only RD with HAQ levels above the average of the population was associated with early retirement, while all those non-RD or RD with lower HAQ scores were non-significant or even inversely associated (Appendix 4). This reinforces the idea that although there is an effect of clinically confirmed RD in early retirement, that effect is "diluted" by mild RD cases with none or mild disability.*

Of note, the chosen age-group for this research was considered the most adequate one due to the following main reasons: 1) It is obviously the age group in the vicinity of official retirement in most developed countries; 2) The most explored age-group in the literature; 3) Narrowing the age-group is itself a method to restrict confounding by age; 4) It also reduces some potential overestimation of early retirement due to right censoring (i.e. more time for potential return to work until all participants reach the official retirement age); 5) Finally, it is the most appropriate age-group to prioritize and intervene when it comes to find and act upon employees at risk. Surely, along with a smaller sample size, a downside of this restriction is a possible underestimation of the association and the impact of RD in early retirement, because younger cases of RD-related job withdrawal were excluded. On the other side, it is also true that the vast majority of disabling RD forms have their onset of symptoms at relatively advanced ages. In fact, this relates with one of the main limitations of this sort of cross-sectional studies, which is reverse causation, as further discussed below.

Despite the age-group considered, OA was not independently associated with early retirement *stricto sensu*, however some OA patients (4.7%) indeed reported to have retired earlier due to RD (which is above the average of global population and the non-OA one [2%, p=0.009], but bellow the self-reported RD group [9.7%], which consistently presented a stronger relationship with this sort of premature retirement). These findings seem to be aligned with the overall pattern of the literature. In a systematic review, Bieleman HJ *et al.* described on one hand that many workers with OA do not reach their optimal productivity during work, which may impact overall work participation, while, on the other hand, OA seems to be responsible for early retirement only in a small proportion of workers.[209]

Surely, OA patients who claimed to have retired earlier due to RD might have done so not specifically due to OA, but rather as a consequence of previous or other concomitant RD. However, if we are to assume that this productivity loss is fully associated with OA, we would calculate a total indirect cost of €237M, a much lower figure even adopting a non-conservative assumption and certainly more comparable to the €910M figure obtained for the whole self-reported RD in EpiReumaPt (Table 4).

As it occurred before with self-reported RD, a higher educational level was linked with at-work status (with the exception in the INS database using official retirement as the outcome). This finding is consistent with many other previously published studies. For example, in 2013 Schuring M *et al*. observed in a prospective study that participants with low to intermediate education had the highest risk of unemployment or early retirement.[98] In the same year, Robroek SJ and colleagues, using the SHARE survey verified that participants with low educational level were more likely to exit from work through a disability pension, unemployment, and early retirement.[120] Higher education generally means higher income and accumulated assets which prone the individual to afford retirement penalties. However, it might be also associated with better workplace conditions, higher motivation and job satisfaction.

A study has shown that if employees are dissatisfied with their job, the probability of retiring earlier is twofold compared with that of satisfied employees.[105] In addition, less educated workers may be subjected to a more stressful physical and psychosocial work environment. Exposure to the latter work environment is typically measured by two established theoretical models: the demand–control[227, 228] and effort–reward imbalance models.[229, 230] In the former, job control denotes the employees' authority to make decisions concerning their own activities and using their skills at work, while job demands refer to time pressures and workload. A combination of high job demands with low job control is assumed to be stressful. The second model focuses on the work contract and emphasizes social reciprocity. Rewards received in return for efforts spent at work include income and career opportunities. The lack of reciprocity (high effort in combination with low rewards) may have a negative impact in retirement decisions, since the basic principle of social exchange, reciprocity, is violated under such conditions. Indeed, Siegrist J *et al*. have shown that poor psychosocial quality of work is significantly associated with intended early retirement.[104] It would be interesting to measure the interplay between educational level, quality of work and risk of retirement in Portugal, due to the likely connection between them.

Less educated workers may also have less access to diagnosis and treatment, which may lead *per se* to ill-health pressure in the ability to work, and to reduced self-perception about health status and self-efficacy at work. In addition to all this,

lower education levels generally lead to manual type of work, which in turn may influence work participation levels, although in INS we didn't find this factor to be independently associated with early retirement (unfortunately, registry errors made it unfeasible to test this factor in the EpiReumaPt database).

Findings concerning other cofactors used in our multivariable regression models weren't as consistent as the educational level. Comorbidity, for instance, aside the fact of its general unquestionable impact, had dissimilar results in the models that were developed in our research when it came to analyse specific diseases. This is mostly due to the fact that the set of cofactors, and thus their relationship in the multivariable models, didn't remain the same from INS to EpiReumaPt. Yet, it can also be a result of a true change on the effect of a given disease in the work ability and/or in the effective retirement throughout time. Cancer, for instance, seems to have lost the magnitude of effect over early retirement. This evolution seems somehow counterintuitive from an epidemiologic angle, because despite the improvements on premature detection and oncology treatment, the overall burden and incidence of cancer has increased,[231] and from a legal point of view there were some legislative steps after 2005-2006 aimed to increase social security for cancer patients.[232] Once again, a *vis-à-vis* comparison of EpiReumaPt with INS must be done prudently, but it would be important to better understand if for some reason cancer patients are facing difficulties to be granted early retirement when needed.

Still regarding comorbidity, mental diseases (which included depression, anxiety, schizophrenia and bipolar disorder) appear to have a role in retirement due to RD, but not general retirement. Higher frequency of some mental distress, such as anxiety and depression, has been associated with some forms of RD,[233,234] but in fact EpiReumaPt study only found a significantly higher proportion of Portuguese RD patients with anxiety symptoms but not with depressive symptoms.[23] In our first approach with INS we specifically tested the role of self-reported depression and anxiety and didn't find any independent association with the outcome. Portugal has one of the highest prevalence of mental disorders in the western world,[235] in particular chronic anxiety and depression, a leading cause of disability worldwide.[236,237] However, these psychiatric disorders don't seem to push *per se* sufferers into early retirement, contrary to what occurs in other countries.[101,126] Alavinia SM *et al*. concluded that in several European countries depression was the

most important health problem associated with main labour force exit. Yet, because it was out of the scope of this study, we cannot rule out that an in-depth analysis with dedicated adjustment could have led to findings in Portugal distinct from ours (of note, as with most studied comorbidities, we found significant univariable ORs for anxiety and depression). Also, this scenario might have changed after 2005-2006, especially following the psychological distress elicited by our sovereign debt crisis. Regrettably, antidepressive use and suicidal rates, particularly bellow 65 years old, have been rising.[238,239]

In EpiReumaPt database we addressed self-reported mental disease as a whole and found an independent association with early retirement due to RD. It would be interesting to further understand this "additional" effect of psychiatric disturbances and to know whether if it was driven by the prevalent forms (i.e. anxiety and depression), the severe ones (e.g. schizophrenia and bipolar disorder) or both.

Anticipating discrimination in the work place[240,241] may lead employees with mental disability to not disclose their condition and it may well be that our cultural and social system is (implicitly) discouraging patients to use mental disability as a primary reason for retirement, as a result of shame, stigmatization and lack of societal valorisation regarding these health conditions. More attention should take place in order to detect eventual cases of RD taken as an "alibi" for the official reason to achieve retirement, while the real causation may lay on mental illness, which obviously requires a completely different approach in terms of possible interventions to postpone work exit.

Definitely, this relationship between mental diseases and early retirement is particularly vulnerable to reverse causation, due to the negative psychological effect that retirement may have in some people. Moreover, justification bias can also take place if some EpiReumaPt participants justified their retirement on the grounds of physical disability when actually the undermining reason was of psychiatric nature. All in all a thinner analysis about the role of mental diseases in early retirement certainly deserves dedicated research in our country.

Still on a last remark about comorbidity, neurologic diseases were strongly associated with early retirement in the EpiReumaPt study (i.e. both sub-studies with

self-reported RD and clinically confirmed OA). This self-reported group of illnesses included stroke, which possibly have driven these findings *per se*, being particularly frequent in the Portuguese population[242] and highly disabling. Actually, in the INS study, where stroke was analysed separately, a strong correlation with early retirement was established.

A major limitation in our research stems from the cross-sectional design of the surveys. This did not allow to accurately evaluate the temporal relationship between onset of risk factors, namely RD, and time to premature retirement, which is a basic element to establish a cause–effect relationship, according with the classic Bradford Hill criteria.[243] In fact, temporality is the most jeopardized criteria among this list of causality criteria. The analysed causal chain has *plausibility*, as depicted in the adopted conceptual model, which in turn is based on the available literature. We observed good *strength* of association between RD and early retirement, which showed *consistency* when using distinct databases, study populations and time points; and *coherence*, with findings compatible with existing theory and knowledge. We also found *specificity* by analysing OA as a particular form of RD. We detected *dose-response relationship* (*biologic gradient*) in the studied causal chain by observing how levels of pain and disability evolved along with the likelihood of being out of work. The remaining 2 criteria, *analogy* and *experiment* could be found in the literature. It is possible to find analogy with other examples of ill-health models where the causal-effect with early retirement, through impairment and disability, has been established elsewhere, as described in the General Introduction. Likewise, some experiments have successfully tested the effect of better disease control of at-risk RD patients on early retirement. As mentioned before, the Abásolo L *et al*.[244] study is a paradigmatic example of such experiments, as well as others described in the 3rd Part of Section B of this thesis.

It is true that with INS the temporal bias was impossible to eliminate, however the EpiReumaPt study obviated, at least to some extent, such limitation, because participants were directly asked whether their retirement was due or not to any health condition, in particular RD. Conversely, this type of self-reported data might be subject to other sorts of bias, such as memory and justification bias, but without any doubt it brought a crucial temporal dimension to our research, thereby mitigating

potential inferences based on temporal bias. On top of all this, the onset of most forms of RD, including OA, are likely to start at an age when people are still working, which also reduces the likelihood of reverse causality.

As previously discussed, our data is mainly self-reported by the participants which is an approach limited by its dependence on the subjectivity of responses. Indeed, the accuracy of data obtained via self-report questionnaires is relatively low compared with that gathered from other sources, for instance medical records or insurance claims.[245] It may produce misclassification bias, as already discussed regarding the case definition of the exposure variable. Also, respondents may overstate symptoms in order to make their situation seem worse, or instead may under-report the severity or frequency of symptoms in order to minimize their problems (i.e. patients in denial). They also may simply be misunderstanding the question, the listed option of responses, be mistaken or misremembered.

Major flaws of memory may be of several types[246] and can trigger one of the most renowned epidemiological bias, the so-called memory bias. Surely, our findings might have been influenced by this systematic error (e.g. age of early retirement), but no better alternative can be found in the available Portuguese databases. Besides, for comparison purposes, most studies, which set the quality standards on this area of research, were also based on self-reporting data and also subject to memory bias. For instance, the European study on ageing and retirement, SHARE project, was founded on self-reports, including its participants' work status. Despite all this, we also used some clinically confirmed data (e.g. OA diagnosis and KOOS scale applied by the rheumatologists) and we verified consistency and reliability in the overall results, namely the general conclusions that may be retrieved with self-reported RD and clinically confirmed OA.

Other limitations have been specifically addressed in the articles, namely those related with the measurement of indirect costs and the adopted human capital approach.

Despite all the addressed cofactors, hidden confounding may have still remained. It is possible that both RD and early retirement are being induced by unobserved heterogeneity of relevant risk factors, such as particular events, social circumstances or health conditions early in life, that were not captured in the surveys. However,

virtually, all association studies are subject to this limitation. It is impossible to control to every single possible confounder, especially with such multifactorial outcome. Given the internal consistency of our results and how they relate with the literature, it seems very unlikely that unobserved confounding is dramatically affecting our findings. In fact, we realized that our study might be among one of the studies examining this subject with higher number of addressed cofactors.

To our knowledge this is the first study specifically to address the association of health and early retirement in Portugal and one of the few in Southern Europe using nationwide surveys. Our results are representative of the country's population and the measured consequences or RD-related retirement are to be taken under the perspective of the whole Portuguese society (high external validity). Using the INS database allowed a first approach with the most prominent health survey performed in Portugal, which is a known tool used to set up the national health policies. It gave a very good initial sense about the association of ill-health and RD with early exit from work and a first result about its impact. While EpiReumaPt, the first nationwide RD survey, permitted an in-depth analysis with more RD-specific data. More than an update of the INS results, EpiReumaPt provided complementary information and in some cases more accurate results, indirect costs being the best example of this. EpiReumaPt also serves as a knowledge platform to promote awareness for the impact of RD as well as setting the ground for better research on these topics, namely through the foundation of the longitudinal project CoReumaPt.[51]

Among many other objectives, CoReumaPt will allow better information about RD progression and its role on employment transitions in Portugal. It may also serve as a platform to test interventions aimed to reduce retirement caused by RD.

In the last part of this study, we reviewed the current knowledge about interventions aiming to reduce early retirement of RD patients. We identified several published studies testing pharmacologic and non-pharmacologic vocational rehabilitation interventions, but none was specifically identified for Portugal. We found many studies addressing the subject but the general low quality of the literature and its inconsistency made it unfeasible to draw definitive conclusions.

Nevertheless, some broad recommendations were outlined. An effective intervention must: 1) act upon different levels (e.g. RD patient, workplace), involving several stakeholders; 2) prioritize the right patients (e.g. more disabling RD); and 3) consider the patients' role, for instance by including an element of patient education and support.

Pharmacologic interventions appear to be supported by more compelling evidence about their effectiveness than non-pharmacologic ones. Cost-effectiveness analysis of new, and in some cases older, drugs should take this in consideration, because, as it is recommended by almost all guidelines for economic evaluation, including the Portuguese, all possible benefits and cost-offsets should be encompassed in such analysis in order to adopt an holistic societal approach, entering indirect costs (productivity gains and losses).[247]

The non-pharmacologic intervention approach must be taken very seriously by healthcare deciders, due to its enormous potential outcome. It is true that it lacks compelling evidence about its impact, but "beyond the pill" programs, such as work adaptations, allied with an appropriate disease management may deliver optimal results in terms of medium to long-term occupational yields. In fact, such multilevel approach could be followed-up in the RD patient registry and cohort already in place in Portugal - Reuma.pt and CoReumaPt. Leveraging the Apto.PT (Fit for Work Portugal)[x] initiative should occur too, in order to foster potential integrated solutions implemented in our country. On the one hand, we have to admit and reiterate the need for more evidence around this subject, but on the other, we also have to understand that decision-making that waits for the "perfect" information may be too costly to afford.

We presented in this thesis the price of inertia, a scenario that is certainly not going to improve if nothing is done otherwise. It seems that a seamless approach would be the most appropriate one – Interventions that theoretically may work out, based on the available literature (herein listed in the 3rd part of Section B of this thesis) and experts' opinion (e.g. consensus composed by rheumatologists, other healthcare

[x] Apto.PT is the Portuguese coalition of the Fit for Work, which is a multi-stakeholder initiative, driving policy and practice change across the work and health agendas in Europe and worldwide (over 35 countries). The vision is to raise awareness of the facts of RD and make the case for more investment in sustainable healthcare by promoting and supporting the implementation of early intervention practices. Fit for Work is led by The Work Foundation – Lancaster University, which is also providing the Secretariat. AbbVie is founding sponsor since 2008. All the research is produced independently by The Work Foundation, with full editorial control resting with the think-thank alone.[xi]

providers, epidemiologists, and other relevant public health and occupational professionals), should start as soon as possible along with “piggy-back” research, which will survey respective effects. Lessons learnt along the way would shape this adaptative intervention.

CONCLUSIONS & FUTURE PERSPECTIVES

Our study found that in Portugal self-reported RD are associated with early exit from paid work, specifically early retirement. Currently, there is an expressive number of people who claimed to be retired prematurely due to RD. This translates in many years of working life already lost and many others still potentially to be lost. Indirect costs due to self-reported RD are also substantial, equivalent to at least 0.5% of GDP. By specifically analysing OA, the most prevalent and disabling joint disorder, we realized that the productivity loss due to RD is potentially even higher than the one obtained when analysing self-reported RD as a whole. Regardless the exact magnitude of the estimates, it seems undisputable that the foregone productivity caused by RD is enormous.

If nothing is done otherwise, this scenario will worsen since the expected increase in the prevalence and impact of some forms of RD. In the future, ageing of the population is expected to make OA a leading cause of disability worldwide. It is true that primary prevention of RD is still difficult to attain, but at least, from a pure clinical standpoint, early diagnosis and effective treatment must be guaranteed in order to mitigate RD pain, impairment and disability, to improve the individual's quality of life and to adjourn major societal costs, namely as a result of early retirement. The current expansion of the rheumatology network in our NHS will certainly have an effect on this regard. In addition to the crucial clinical approach, other sorts of interventions shall take place beyond but articulated with the NHS. Intersectorial collaboration is a key topic embedded in the current National Health Plan (PNS, *Plano Nacional de Saúde* 2012-2016). [248] Several collaborations between the Portuguese Ministry of Health and the Ministry of Labour, Solidarity, and Social Security were built,[249] but none seems to target vocational interventions aiming to reduce early retirement and certainly not being specific of RD. This perhaps arises from the fact that the Health in All Policies (HiAP) mind-set, endorsed by WHO, mostly targets the effects on health from other sectors within the government, rather than the opposite. HiAP is an approach to public policies across sectors that systematically takes into account the health implications of decisions, seeks synergies, and avoids harmful health impacts in order to improve population health

and health equity. It improves accountability of policymakers for health impacts at all levels of policy-making. It includes an emphasis on the consequences of public policies on health systems, determinants of health and well-being.[250] However, given the joint effort and the synergies built to reach common goals centred on the community's health it would also make sense to take advantage of this timing and momentum of political and societal will to include retirement due to illness in the agenda as well, particularly for RD. Moreover, in Portugal as in other countries, a recent policy response to increasing life expectancy and the sustainability issues faced by social security was to rise the age at which pensions can be accessed. Delayed access to a pension might be mostly challenging for individuals with poorer health. This might be particularly true for those of lower socioeconomic status who, in addition to being more likely to have substantial health problems, including suffering from a RD, often work in the most physically demanding jobs and have the fewest alternative job opportunities. This concern has to be thoroughly addressed in the Portuguese political agenda, which should get the compromise from the relevant sectors of society and from the Ministries which overrule them, just as recognized by the HiAP approach.

From a tactical point of view, multistakeholder vocational interventions could be implemented in a step-wise manner in Portugal. It is somewhat difficult to recommend an "already-made" program expected to be inevitably effective, but this fact cannot justify inertia in this field – it is overly costly. Thus, pilot projects can be conceptualized and implemented by experts in the field, including rheumatologists, epidemiologists and occupational specialists, and then, if proof-of-concept is achieved, further expansion could occur throughout the Portuguese territory. This implies that effectiveness of such interventions must be collected through piggy-back studies, preferably of longitudinal design.

One of the main caveats of our study was the lack of longitudinal assessments within the same study population. It is therefore important to build long-term cohorts aiming to collect occupational and health information. On this regard we already designed the CoReumaPt – the cohort of RD in Portugal. In 2011, anticipating the needed longitudinal follow-up of RD patients concerning relevant outcomes, including occupational ones, we started the CoReumaPt project (Appendix 5). In the future, this will allow understanding more closely the relationship between RD and early

retirement throughout the time and the course of the disease. It also may be the basis to test the effectiveness of the aforementioned vocational interventions.

Longitudinal studies may also help to study less prevalent RD, such as RA, and the respective impact on the employment status. Multiple within-subject assessments might allow overcoming the lack of statistical power which hampers cross-sectional studies, especially when multivariable regressions are required. Thus, this might help building a final “global picture” about the economic impact of RD, as the sum of estimates from the most impactful RD forms, based on the same epidemiologic platform.

In the future, it will also be relevant to study other sorts of costs (e.g. direct costs) in order to sum up the whole economic impact of RD in Portugal. Our findings contribute with the RD-related early retirement, but a full RD cost-of-illness analysis, using a bottom-up approach founded on the individual observations of EpiReumaPt and CoReumaPt, is of paramount importance for Portugal and for the prioritization of its public health policies. Such data is also critical for other major chronic diseases, for which there is still a significant lack of nationwide epidemiologic data. In fact, epidemiologic studies like EpiReumaPt for other chronic diseases are still largely missing in our country.

Cost-of-Illness information is essential *per se*, but it is also fundamental to support other kinds of evaluations, such as the cost-effectiveness of new pharmaceutical drugs, just as the growing field of Health Technology Assessment (HTA), within a system, more than ever, needing for increased efficiency.

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APPENDICES

APPENDIX 1

Linktest of main Logistic Regression Models

Model predicting Early Retirement in INS (Article A):

```
Number of strata   =         7                  Number of obs      =      6052
Number of PSUs     =      6052                  Population size    = 1859144.9
                                                 Design df          =      6045
                                                 F(   2,   6044)    =    198.12
                                                 Prob > F           =    0.0000
```

Tipo1	Coef.	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_hat	1.019121	.1116772	9.13	0.000	.8001934	1.238048
_hatsq	.0082095	.0412983	0.20	0.842	-.0727498	.0891687
_cons	.0038729	.0749164	0.05	0.959	-.1429899	.1507357

Model predicting Early Retirement in EpiReumaPt (Article B and C):

```
. linktest
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =     10661
Number of PSUs     =     10661                  Population size    =   8081109
                                                 Subpop. no. of obs =      2792
                                                 Subpop. size       = 1706749.8
                                                 Design df          =     10660
                                                 F(   2,  10659)    =    143.60
                                                 Prob > F           =    0.0000
```

TIPO1	Coef.	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_hat	.9808954	.1063604	9.22	0.000	.7724092	1.189382
_hatsq	-.0120573	.044439	-0.27	0.786	-.0991661	.0750515
_cons	.0081418	.0934199	0.09	0.931	-.1749785	.1912622

Model predicting Early Exit From Work in EpiReumaPt (Article D):

```
. linktest
(running logit on estimation sample)

Survey: Logistic regression

Number of strata   =         1                  Number of obs      =      3874
Number of PSUs     =      3874                  Population size    =   8078720
                                                 Subpop. no. of obs =      1283
                                                 Subpop. size       = 1706746.5
                                                 Design df          =      3873
                                                 F(   2,   3872)    =     36.31
                                                 Prob > F           =    0.0000
```

TIPO3	Coef.	Linearized Std. Err.	t	P>|t|	[95% Conf.	Interval]
_hat	1.06047	.1313327	8.07	0.000	.802982	1.317958
_hatsq	-.2458921	.1282974	-1.92	0.055	-.497429	.0056448
_cons	.1347801	.1592515	0.85	0.397	-.1774447	.447005

APPENDIX 2

Comparison of Self-Reported RD and Clinically Confirmed RD (Quality of Life and Function)

	Self-Reported RD*	Clinically Confirmed RD**
Score HAQ (*0-3 from best to worst)*	0.57	0.48
EQ-5D *(0-100 from worst to best imaginable health state)*	0.67	0.73
SF-36 physical function *(0-3 from worst to best)*	63.9	71.4
SF-36 role limitations because of physical health problems	56.0	65.6
SF-36 bodily pain	53.2	59.5
SF-36 social functioning	79.5	82.9
SF-36 general mental health	56.3	62.8
SF-36 role limitations because of emotional problems	67.2	75.7
SF-36 vitality	47.9	54.6
SF-36 general health perceptions	44.9	50.0

RD, Rheumatic Diseases, HAQ, Health Assessment Questionnaire; SF-36, Short-Form Health Survey; EQ-5D, European Quality of life Questionnaire;
**All p-values significant (p<0.001) versus non-RD (self-reported) using the Student's two-tailed unpaired t test.*
*** All p-values significant (p<0.001) versus non-RD (clinically confirmed)*

APPENDIX 3

Diagnostic Tests of Self-reported RD

DR_clin	DR_Auto Pos.	Neg.	Total
Abnormal	**561**	**576**	**1,137**
Normal	**30**	**119**	**149**
Total	**591**	**695**	**1,286**

True abnormal diagnosis defined as DR_clin = 1

			[95% Confidence Interval]	
Prevalence	Pr(A)	**88.4%**	**86.5%**	**90.1%**
Sensitivity	Pr(+|A)	**49.3%**	**46.4%**	**52.3%**
Specificity	Pr(−|N)	**79.9%**	**72.5%**	**86.0%**
Positive predictive value	Pr(A|+)	**94.9%**	**92.8%**	**96.5%**
Negative predictive value	Pr(N|−)	**17.1%**	**14.4%**	**20.1%**

APPENDIX 4

Results for Clinically Confirmed RD (according with different levels of disability)

	Clinically Confirmed RD	RD + ↑ HAQ**	RD & ↓ HAQ***	NON-RD + ↑ HAQ	NON-RD & ↓ HAQ***
Unemployment	2.4 (1.1-5.1)*	1.5 (0.9-2.3)	0.7 (0.4-1.1) NS	2.0 (0.6-6.6) NS	0.5 (0.1-1.7) NS
Early Retirement	0.8 (0.4-1.5) NS	1.7 (1.1-2.6)	0.6 (0.4-0.9)	0.6 (0.1-2.6) NS	1.7 (0.4-7.3) NS
Early Retirement due to Disease	2.3 (0.9-5.7) NS	4.3 (2.6-7.1)	0.2 (0.1-0.4)	1.5 (0.4-5.9) NS	0.7 (0.2-2.7) NS
Early Retirement due to RD	5.3 (1.1-26.0)	10.5 (4.8-22.9)	0.1 (0.0-0.2)	1.0 (0.1-7.7) NS	0.9 (0.1-7.0) NS
Exit from work	1.3 (0.7-2.4) NS	2.4 (1.6-3.6)	0.4 (0.3-0.6)	1.3 (0.4-3.9) NS	0.8 (0.3-2.4) NS

RD, Rheumatic Diseases (clinically confirmed); HAQ, Health Assessment Questionnaire.
*All odds ratios adjusted for age and sex using EpiReumaPt database;
**High HAQ values defined as above the average of the global EpiReumaPt population (i.e. >0.38)
***Low HAQ values defined as below the average of the global EpiReumaPt population (i.e. <0.38)

APPENDIX 5

LIST OF RELEVANT PUBLICATIONS

ARTICLES:

1. **Laires PA**, Gouveia M, Canhão H.
   Interventions aimed at Preventing Early Retirement due to Rheumatic Diseases.
   Acta Reumatológica Portuguesa. Ago 2016 (submitted).

2. **Laires PA**, Canhão H, Rodrigues A, Eusébio M, Gouveia M, Branco JC.
   Early Exit From Work Attributable to Osteoarthritis and its Economic Burden.
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3. **Laires PA**, Gouveia M, Canhão H, Branco JC.
   The Economic Impact of Early Retirement Caused by Rheumatic Diseases - Results from a Nationwide Epidemiologic Study.
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4. Branco JC, Rodrigues AM, Gouveia N, Eusébio M, Ramiro S, Machado PM, da Costa LP, Mourão AF, Silva I, **Laires PA**, Sepriano A, Araújo F, Gonçalves S, Coelho PS, Tavares V, Cerol J, Mendes JM, Carmona L, Canhão H.
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APPENDIX 6

CoReumaPt Protocol:

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Acta Reumatol Port. 2012;37:18-24

CoReumaPt Protocol: the Portuguese Cohort of Rheumatic Diseases

Pedro A Laires[1], Helena Canhão[2], Domingos Araújo[3], João Eurico Fonseca[4], Pedro Machado[5], Ana Filipa Mourão[6], Sofia Ramiro[7], José Carlos Romeu[8], Maria José Santos[9], Inês Silva[10], José A Pereira Silva[11], Elsa Sousa[12], Viviana Tavares[13], Nélia Gouveia[14], Jaime C. Branco[15]

ACTA REUMATOL PORT. 2012;37:18-24

ABSTRACT

Introduction: Rheumatic diseases (RD) are conditions with a variety of clinical manifestations and prognosis influenced by several factors. Cohorts and registries have been already established in some countries and have contributed to important knowledge about the disease course and the long-term outcomes of RD. This paper introduces the CoReumaPt project and sets the first step towards the creation of a prospective cohort study including the main RD occurring in the Portuguese population. CoReumaPt will allow outcomes research of chronic RD and the assessment of factors influencing the development and progression of RD. It will also allow to further evaluate the economic impact and the burden of RD in Portugal. CoReumaPt will be linked to Reuma.pt, the National Register of Rheumatic Diseases from the Portuguese Society of Rheumatology.

Methods: An open cohort will be created, initially composed by the randomly selected population of the cross-sectional National Epidemiological Rheumatic Diseases study (EpiReumaPt) and afterwards by other sources, namely through self- and physician's referral. Follow--up with annual self-administered questionnaires will be performed, in order to systematically collect and analyze outcomes of interest, mainly patient-reported outcomes. Data concerning less frequent assessments, such as radiographs and biomarkers, will also be assembled.

Conclusions: CoReumaPt will be a valuable resource for scientific research and will deliver pivotal information to improve public health policies concerning the prevention and the management of RD in Portugal.

1. EpiReumaPt Research Group; Consultant at Sociedade Portuguesa de Reumatologia.
2. EpiReumaPt Research Group; Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Portugal; Department of Rheumatology, Centro Hospitalar de Lisboa Norte, Hospital de Santa Maria, EPE, Lisbon, Portugal; Harvard Medical School, Boston, USA.
3. Department of Rheumatology, Unidade Local de Saúde do Alto Minho, Ponte de Lima, Portugal.
4. Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Portugal; Department of Rheumatology, Centro Hospitalar de Lisboa Norte, Hospital de Santa Maria, EPE, Lisbon, Portugal.
5. EpiReumaPt Research Group; Leiden University Medical Center, Leiden, The Netherlands; Department of Rheumatology, Hospitais da Universidade de Coimbra, Coimbra, Portugal.
6. EpiReumaPt Research Group; Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Portugal; Department of Rheumatology, Centro Hospitalar de Lisboa Ocidental, EPE/Hospital Egas Moniz, Lisbon, Portugal; CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal.
7. EpiReumaPt Research Group; Department of Rheumatology, Hospital Garcia de Orta, EPE. Almada, Portugal; Department of Clinical Immunology & Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.
8. Department of Rheumatology, Centro Hospitalar de Lisboa Norte, Hospital de Santa Maria, EPE, Lisbon, Portugal.
9. Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Portugal; Department of Rheumatology, Hospital Garcia de Orta, EPE. Almada, Portugal.
10. EpiReumaPt Research Group; Department of Rheumatology, Centro Hospitalar de Lisboa Ocidental, EPE / Hospital Egas Moniz, Lisbon, Portugal.
11. Department of Rheumatology, Hospitais da Universidade de Coimbra, Coimbra, Portugal; Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal.
12. Rheumatology Research Unit, Instituto de Medicina Molecular da Faculdade de Medicina da Universidade de Lisboa, Portugal; Department of Rheumatology, Centro Hospitalar de Lisboa Norte, Hospital de Santa Maria, EPE, Lisbon, Portugal.
13. Department of Rheumatology, Hospital Garcia de Orta, EPE. Almada, Portugal.
14. EpiReumaPt Research Group; Sociedade Portuguesa de Reumatologia.
15. EpiReumaPt Research Group; Department of Rheumatology, Centro Hospitalar de Lisboa Ocidental, EPE / Hospital Egas Moniz, Lisbon, Portugal; CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisbon, Portugal.

Keywords: Rheumatic Diseases; Cohort Studies; Outcome Assessment; Epidemiologic Studies.

INTRODUCTION

Rheumatic diseases (RD) are complex conditions characterized by a variety of clinical manifestations and prognosis. Cohort studies are one of the best ways to assess and understand the course of these diseases. To complement information obtained from randomized clinical trials, various cohorts and registries of patients with specific RD or other exposures have been established in the last decade (for instance, the Consortium of Rheumatology Researchers of North America [CORRONA] and the British Society for Rheumatology Biologics Register [BSRBR]). Thus, large prospective cohorts have increasingly contributed to pivotal research in the field of RD, which would have been difficult to obtain from other data sources. Actually, they constitute one of the major sources of clinical research publications and communications in rheumatology. Prospective cohort studies describe the disease course and management strategies and record long--term outcomes of the disease. Moreover, they contribute substantially to better understand the pathogenesis and the mechanisms underlying the disease progression. Prospective cohorts also enable the study of associations between disease and treatment interventions. In fact, information derived from such studies can guide the design of future drug trials[1].

Cohorts are organized around conditions or exposures, such as a particular disease, a health care service (e.g. a new medical procedure), or a product (including medical devices). In fact, registries of cohorts are mainly either drug based (e.g. patients enrolled after starting a particular medication) or disease based (e.g. patients enrolled after being diagnosed with a particular disease, such as a certain RD)[1]. They can vary in complexity, from simply recording a product use, as a requirement for reimbursement, to more systematic efforts to collect prospective data on several treatments, risk factors and clinical events in a defined population. Therefore, prospective cohorts allow complete data collection in a deliberate attempt to gather relevant information (i.e. aiming at maximizing measured covariates and minimizing missing information)[4]. The duration of follow-up can range from days (e.g. hospital admission registry) to decades (e.g. orthopedic implant registry or rheumatoid arthritis cohorts)[1].

The Portuguese Society of Rheumatology (SPR) already detains a national register (Reuma.pt) for several rheumatic diseases [rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA)], but so far no further registries of patients with other relevant chronic RD have been undertaken in Portugal, such as, osteoporosis (OP), osteoarthritis (OA), systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), fibromyalgia (FM), gout (GO), periarticular diseases (PD) and non-specific low-back pain (LBP). Several outcome research projects on these RD have been published based on European and North American cohorts. However, different populations have diverse genetic and environmental backgrounds that influence outcomes, such as morbidity and mortality rates. Furthermore, patient's access to healthcare services and the economic burden of these diseases in Portugal have clearly very specific patterns that need to be identified, namely by measuring the healthcare resources consumption and by assembling data concerning absenteeism and presenteeism (loss of productivity). This effort will define the precise social and economical impact of RD, allowing the adaptation of future policies by our National Healthcare System to the identified needs.

The EpiReumaPt survey, is an ongoing Portuguese epidemiologic cross-sectional study (2011-2013) and it has the main aim of estimating the prevalence of different RD in Portugal. The 10000 participants in this project (a random sample of the Portuguese population) will be invited for a long-term follow-up, during which they will be integrated into the CoReumaPt cohort.

This article presents the CoReumaPt study and sets the first step towards the creation of a prospective cohort for the main RD occurring in the Portuguese population.

OVERVIEW OF COREUMAPT

The overarching principle of the CoReumaPt Project is to improve public health through the knowledge and prevention of RD in Portugal. In order to achieve this, a cohort will be created, including chronic RD patients (namely OP, OA, RA, AS, SLE, PMR, FM, GO and LBP) and "non-RD" subjects. This large cohort might be afterwards divided in specific cohorts according to the future development of this project. The link with Reuma.pt will be done; patients with a confirmed diagnosis of RA, spondyloarthritis (SpA, including AS and

PsA) or JIA will be also invited to enroll the ongoing register of patients with these diseases, in case they are not already participating.

OBJECTIVES OF COREUMAPT

PRIMARY OBJECTIVE

To establish open cohorts to further explore outcomes research of chronic RD and the risk factors for the development of RD.

SECONDARY OBJECTIVES

1. To estimate the incidence of health outcomes in different RD according to clinical and socio-demographic characteristics.
2. To evaluate prospectively the impact of different RD at the individual (clinical and humanistic consequences) and social level (including economic consequences).
3. To estimate the contribution of prognosis factors to the progression of RD in the Portuguese population.
4. To determine the burden of different RD on the functional capacity and work participation of the Portuguese population.
5. To monitor the effectiveness and safety of current RD treatments in a "real-world" setting.
6. To identify regional differences across the country for the abovementioned endpoints.
7. To compare the incidence of relevant outcomes with other countries.

METHODOLOGY OF COREUMAPT

STUDY DESIGN

Population-based multi-disease, multipurpose cohort study.

STUDY POPULATION

The study population source is described in more detail elsewhere[7] and is composed by Portuguese non-institutionalized adults (≥ 18 years old) randomly selected in the EpiReumaPt study and who voluntarily agreed to participate by signing a written Informed Consent. In parallel, other sources of patients might be used, for instance, physician's referral or patient's self-referral, as long as validation by a rheumatologist occurs prior to the inclusion in the cohort (Figure 1).

All enrollees must also be mentally competent, as defined by the opinion of the investigator or rheumatologist, in order to be able to participate in all study required assessments and procedures. Subjects unwilling to sign the Informed Consent, unable to speak Portuguese or with an inability to answer the questionnaire will be excluded.

PRIMARY OUTCOMES

This study will be designed to systematically collect and analyze longitudinal outcomes. Herein is the list of the "core" outcomes of interest a priori targeted for this cohort. Later, specific domains will be addressed for particular groups of subjects (e.g. specific measures of disease activity and physical function). These specific domains will be detailed in future publications.

Thus, a core set of outcome measurements (clinical, laboratory and imaging) will be assembled at baseline and follow-up. Questionnaires will be designed to be mainly self-administered by the participants (i.e. patient-reported data) and cover most of the outcomes outlined in Figure 2. Questionnaires will also address socio-demographic factors, life-style factors and exposure variables.

The selection of primary outcomes for measurement in this study has been accomplished considering the

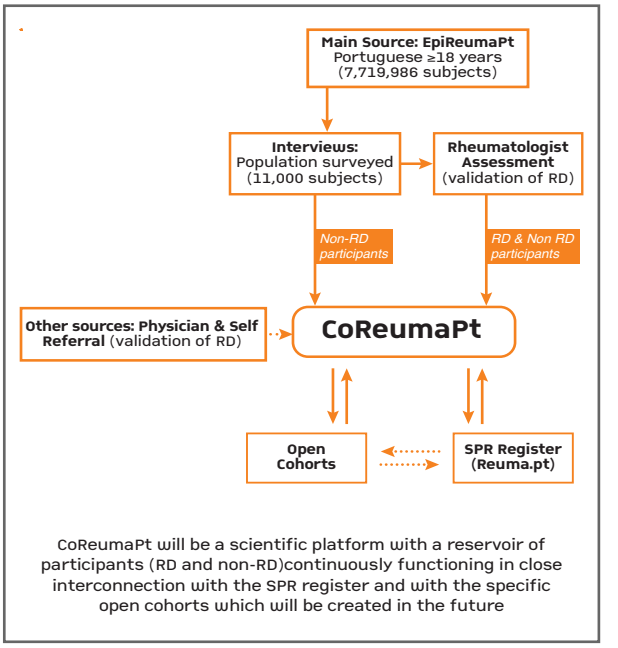

Figure 1. CoReumaPt study population and due participants' flow

RD: Rheumatic Diseases

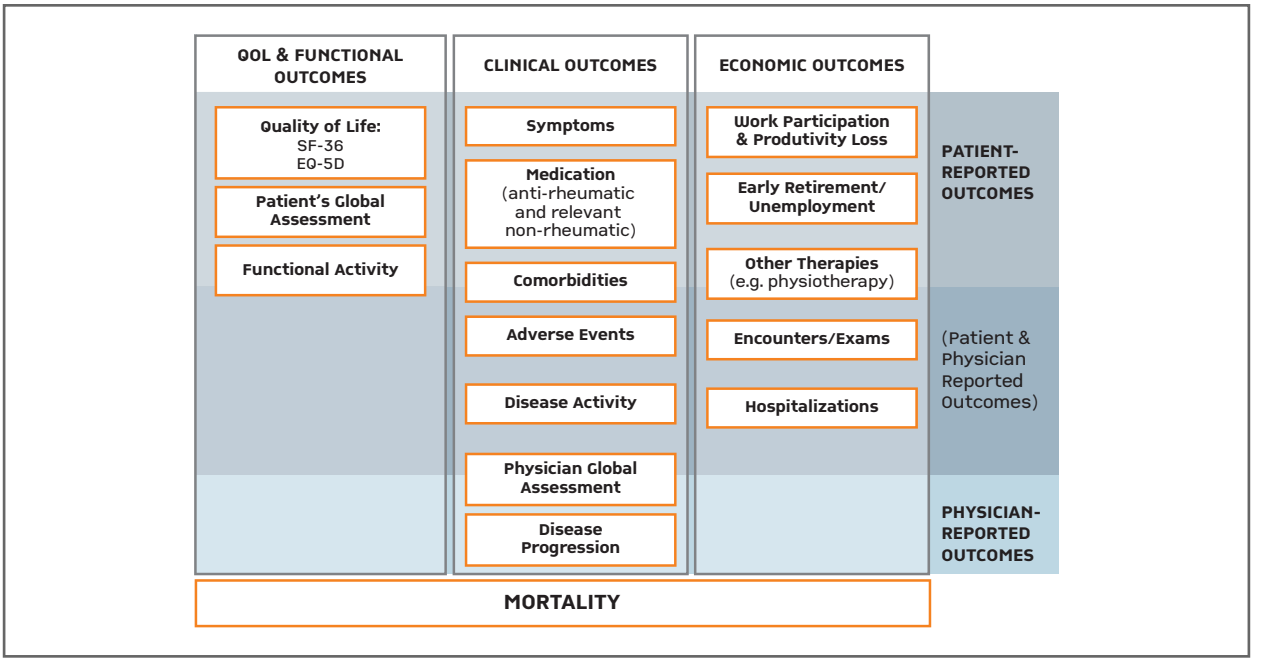

Figure 2. Primary Outcomes to be addressed in the CoReumaPt study

QoL: Quality of Life; SF-36: Short Form (36) Health Survey; EQ-5D: EuroQol-5D

OMERACT (Outcome Measures in Rheumatology Clinical Trials) consensus process.

STUDY PROCEDURES

INITIAL PATIENT ENROLLMENT AND PHYSICIANS' PARTICIPATION

Following each subject's selection and participation in the EpiReumaPt cross-sectional study, an assessment of the willingness to be followed-up and due involvement in the subsequent cohort phase will be done, which includes an Informed Consent and collection of information contact. Within 3-6 months, the participant will be contacted again by the study staff via phone call in order to confirm willingness to be followed-up and to obtain additional data. The enrollee will also be inquired about his preferred method of contact (phone, paper-based or web-based). Repeated unsuccessful contacts may lead to the participant's dismissal from the cohort.

In this first assessment, the participant will be given details to access a web-based platform (including a username and a password), which is meant to be the preferred method for patient-data collection during the follow-up period. Phone calls and questionnaires sent by post during follow-up will be alternative ways to collect data if requested by the participant or to complete information provided via online questionnaires (Figure 3).

Identified physicians clinically in charge for a given participant will also be invited to participate in this study; thereby receiving details for the access to the web-based platform, and also getting their patients' identification codes. Physicians will be requested to complete some baseline information (e.g. disease activity) and also yearly updates on other relevant clinical information, complementary to the patient-reported data (see below Annual Questionnaire). Physicians will also be requested to validate some patient-reported outcomes (PRO) (e.g. hospitalizations and serious adverse events).

FIRST CONTACT - BASELINE ASSESSMENT

The majority of the baseline data will be provided by the EpiReumaPt study, however CoReumaPt baseline assessment will collect more detailed medical history, such as past hospitalizations, past and current comorbidities, medications and adverse events. Any hospitalization occurring within the past 12 months and self-reported by the participant should be validated through medical records or by contacting the respecti-

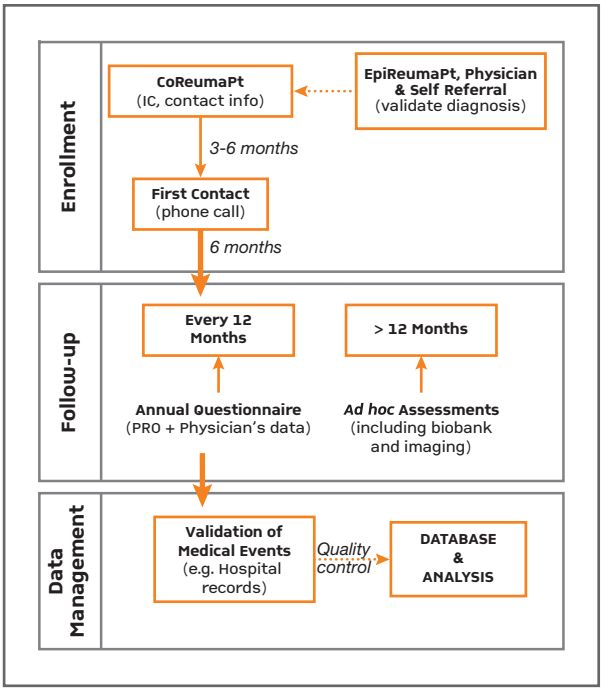

Figure 3. Flow diagram of CoReumaPt processes and follow-up assessments

IC: Informed Consent; PRO: Patient-Reported Outcomes

ve hospital or the physician. Other up-to-date PRO will be addressed, such as health-related quality of life, functional status and work disability. For further economic analysis, healthcare resources utilization (such as medical encounters and exams) should be registered at the baseline assessment. After finishing this contact, scheduling of the next one will be done (Figure 3).

ANNUAL QUESTIONNAIRE – PRO AND PHYSICIAN-REPORTED DATA

At 12-month intervals, CoReumaPt participants will be surveyed by a self-administered questionnaire. This questionnaire shall bring together information regarding PRO and the clinician-reported data (Figure 3).

All physicians will be reminded to include data concerning the closest visits of their patients. Physicians will be requested to revise all patient-reported fields (including medication and adverse reactions) and, more importantly, will be asked to fill in clinical data related with the physician's evaluation (including disease activity). Both patients and physicians (if applicable) will also be requested to record all hospitalizations, medical encounters and other relevant healthcare resource consumption occurred in the past 12 months.

New RD cases among the "non-RD" participants will be captured through self-report of RD diagnosis or rheumatic symptoms. This must be further validated by a rheumatologist.

>12-MONTHS ASSESSMENTS (BIOBANK AND IMAGING EXAMS)

In order to address some outcomes of interest and to further assess the evolution of RDs, some exams will be periodically required (e.g. radiographs to assess structural damage, BMD as measured by DEXA, and laboratory tests). These assessments are disease-specific and their periodicity will depend on the outcomes selected for each specific cohort, which will be described in more detail in dedicated publications. Moreover, for future genetic and biomarkers analysis, blood samples will be drawn at baseline from participants during the EpiReumaPt procedures and afterwards at different time-points along their follow-up. All these samples will be stored at the Biobank of Instituto de Medicina Molecular, Lisbon.

OTHER ASSESSMENTS

Patients and physicians might be asked by the CoReumaPt staff to send the results of some exams with the purpose of validating outcomes of interest (for example, radiographic evidence of OP fractures). This will be done *ad hoc* and driven by the Steering Committee of the CoReumaPt team (see below Steering Committee section). Other data might be requested upon a new scientific question requiring additional data not captured in the original questionnaires. This should also be previously approved by the Steering Committee.

DEFINITION OF RHEUMATIC DISEASES

The participant's exposure to any RD will be assessed by the rheumatologist who will validate the final diagnosis of each participant. This diagnosis of a given RD, either active or in remission, will be based on the internationally accepted classification criteria of that RD and should be aligned with the EpiReumaPt study[7].

INTERNAL/EXTERNAL VALIDITY AND QUALITY CONTROL

An essential requirement for the use of a longitudinal dataset is the internal and external validity of the cohort. Patients without RD should be representative of

the population from which they are drawn, using a random sampling and avoiding selection bias. This issue has been carefully handled in the EpiReumaPt study, which is the primary source of the CoReumaPt, and thus representativeness of the Portuguese Population is expected to be maintained concerning that source of participants. This will be tested by comparing the demographic characteristics of the overall EpiReumaPt population versus the Portuguese population, according to the National Institute of Statistics (INE). Nevertheless, CoReumaPt is an open cohort which will allow further entry of new enrollees. Therefore it is possible that selection bias occurs along the project. This bias and any other eventual deviation will be handled *ad hoc* by the Steering Committee.

In an attempt to avoid any bias based on socioeconomically status, paper-based questionnaires will be sent to those participants without phone or computer devices or; for those who simply prefer to send their responses by post (free-of-charge).

In order to increase internal validity and to provide complete and accurate data, the methods of observation will be clearly defined and the measurement tools will be valid and reliable. All procedures will be standardized and properly documented. The activities designed to achieve proper quality control will encompass all aspects of the study, including: clear, pretested data collection forms; measurements that are validated; central and local training of staff; monitoring of recruitment and retention; surveillance and evaluation of data quality as it is collected. Supervision and ultimate responsibility of quality assurance will rest with the Steering Committee.

Follow-up maintenance is crucial for the success of any cohort study[10], therefore attrition bias will be avoided by using reminders for scheduled visits and implementing specific activities to motivate participation (e.g. periodic newsletters and reminders sent to participants). A specific task-force reporting to the Steering Committee will deal with this bias and will be responsible for activities designed to increase participants' retention in this study. Non-respondents will be tracked in order to ascertain reasons of discontinuation and to fill, whenever possible, a short "end-of-study" questionnaire. Lost to follow-up population will be characterized to detect eventual factors asymmetrically prevalent when compared with more adherent participants. If possible, death records will be consulted for all participants to whom long-term unsuccessful contacts have occurred.

All assessment dates will be reminded to patients and physicians upfront and missing assessments will be followed-up via phone directly by a member of the CoReumaPt staff. Missing data within one assessment will generate automatic reminders both to patients and physicians so that completion could be fulfilled.

Concerning the quality of the database, its content will be audited visually by a person trained to process the forms and a web-based platform will be designed to detect out-of-range values, inconsistencies and missing data, thereby triggering alerts to the CoReumaPt staff.

Any event that results in hospitalization or any critical medical event will be validated by obtaining medical confirmation. Exposure variables will be subject to frequent validation by the Steering Committee of the CoReumaPt, namely the RD exposure. Primary Outcomes will also be subject to the Steering Committee's evaluation, especially those requiring radiographic confirmation.

REGISTRY SIZE AND DURATION

There is no limit set regarding the cohorts' size. For the time being, size will depend on the EpiReumaPt participants' willingness to be followed-up. Since this is a multipurpose cohort study there is no a priori definition for its duration. It will depend on several factors, including funding and enrollees' availability and willingness to persist on study.

ETHICAL CONSIDERATIONS

This project was approved by Comissão Nacional de Protecção de Dados, the Portuguese data protection authority (in accordance with the Portuguese law number 67/98, October 26th, regarding protection of personal data) and was submitted to the Ethics Committee of the Faculty of Medical Sciences from the Universidade Nova de Lisboa. The study will be conducted in accordance with the applicable laws and regulations including, but not limited to, the Guideline for Good Clinical Practice (GCP) and the ethical principles stated in the Declaration of Helsinki.

Participants' confidentiality will be safeguarded by the nonexistence of identifiers on the database (only unique ID participants' codes). Their names and contacts will be stored separately from study data trans-

mitted to the coordinating center (based on the headquarters of the SPR). Thus, all data for future analysis will be kept anonymously and securely by the CoReumaPt authorized staff.

All participants will sign an Informed Consent before enrollment, thereby authorizing further follow-up for collection of personal and clinical data. For the Biobank future research purposes, a specific Informed Consent will also be signed by those accepting to participate in this part of the CoReumaPt study.

For all paper-based questionnaires, transcription for the electronic system will be done by authorized personnel complying with all confidentiality procedures of the study. The electronic dataset will then be associated with the participants' ID code.

There will be absolutely no disclosure of individual health information to the general public. Thus, publications will be strictly confined to aggregated data.

STEERING COMMITTEE

The Steering Committee will be the primary governing body of the study and provides its scientific leadership. It will have responsibility for the overall study design, policy decisions and operations of the CoReumaPt study. As abovementioned, the Steering Committee might decide upon the request of additional data (e.g. laboratory exams, imaging) as needed. Members of this Steering Committee will include national rheumatologists, epidemiologists and statisticians, as well as international consultants thoroughly experienced with previous cohort studies.

Among the Steering Committee there will be investigators responsible for future specific cohorts. Thus, a given leading coordinator will be accountable for the oversight and the selection of the outcomes assigned to each specific cohort. Nominations for this coordination and all changes in the protocol will be subject to majority vote of the Steering Committee. This Steering Committee will be chaired by the SPR board and a record of changes and decisions will be maintained by SPR.

ACKNOWLEDGEMENTS

The authors acknowledge Prof. Henrique de Barros (Faculdade de Medicina da Universidade do Porto, Portugal), Prof. Daniel Solomon (Brigham and Women's Hospital, Harvard Medical School, Boston, USA), Prof. Robert Landewé (University Hospital Maastricht, the Netherlands) and Prof. Loreto Carmona (Sociedad Española de Reumatología, Madrid, Spain) for their critical suggestions which contributed to the improvement of this protocol.

CORRESPONDENCE TO

Pedro Almeida Laires
Sociedade Portuguesa de Reumatologia
Avenida de Berlim, 33B, 1800-033 Lisboa
E-mail: coreumapt@spreumatologia.pt

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